EXHIBIT D

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

IN RE: '318 PATENT INFRINGEMENT LITIGATION	)	Civil Action No. 05-356-KAJ (Consolidated)

SECOND EXPERT REPORT OF DR. JEFFREY L. CUMMINGS

I. INTRODUCTION

1. This report supplements my opening expert report of July 28, 2006. In this report, I was asked by Plaintiffs to review the opinions set forth in the reports by Drs. Edward Domino and Allan Levey in this case and to set forth my own opinions concerning the validity of U.S. Patent No. 4,663,318 ("the '318 patent") in view of the defendants' claims that the patent is invalid due to anticipation, obviousness, or lack of enablement.

2. In reviewing the reports of Dr. Domino and Dr. Levey and forming the opinions stated in this report, I have reviewed the Domino and Levey reports, the documents discussed in those reports, and also the materials referenced in my opening report and in Attachment A to this report. Of course, I have also relied upon my experience and knowledge of the relevant literature and state of the art.

II. LEGAL STANDARDS

3. In order to assist me in evaluating the defendants' experts' reports and in forming my own opinion concerning the validity of the patent, I have been informed of the legal standards governing anticipation, obviousness, and enablement.

A. Anticipation

4. I have been informed that the statutory requirement for anticipation of a patent claim is that the claimed invention must be shown to be "known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for patent," 35 U.S.C. § 102(a). I understand that the claimed invention may also be anticipated if the invention has already been patented or has been described "in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of the application for patent." 35 U.S.C. § 102(b). Defendants' experts have asserted that the '318 patent was anticipated by an article published before Dr. Davis applied for her patent — P.A. Bhasker, "Medical Management of Dementia," The Antiseptic 71:45-47, 1974 (the "Bhasker article"). In order for the Bhasker article to anticipate claims 1 and 4 of the '318 patent, I understand that the article must describe the invention claimed in those patent claims. That is, the article must describe, to one of ordinary skill in the art, each and every element of those claims.

5. Moreover, in order for the article to qualify as a "printed publication," I understand that the Bhasker article must be "publicly accessible." That is, it must be accessible to persons skilled or interested in the art. I understand that indexing of the article is relevant to determining whether it was accessible to persons skilled or interested in the art.

B. Obviousness

6. I have been informed that the following factors are relevant in determining whether a patent is invalid for reasons of obviousness: (1) the scope and content of the prior art; (2) the differences between the patented invention and the prior art; (3) the level of ordinary skill in the art; and (4) objective considerations of non-obviousness. I note that objective considerations of non-obviousness were addressed in my opening report. In forming my

opinion, I have also been asked to consider whether the prior art would have provided a person of ordinary skill a motivation to combine or modify the prior art references so as to arrive at the claimed invention and also whether it would have provided such a person with a reasonable expectation of success in doing so.

C. Enablement

7. Enablement: I understand that to be valid, a patent must enable one skilled in the art to make and use the claimed invention. A patent is enabling even if some experimentation is required, as long as it is not unduly extensive.

D. Summary of opinion

8. Anticipation: It is my opinion that the '318 patent is not invalid due to anticipation. The reference cited by the defendants' experts -- the Bhasker article -- does not describe the use of galantamine for the treatment of Alzheimer's Disease ("AD"). In addition, I do not believe that the article would have been accessible to a person interested in treatments for AD, since as far as I (or apparently the defendants) are aware, by January 1986 it was neither indexed nor cited and would not have been found by a person of ordinary skill.

9. Obviousness: It is my opinion that the '318 patent is not invalid due to obviousness. The references discussed in the defendants' experts' reports neither lead one of ordinary skill to the use of galantamine for the treatment of AD nor provide such a person with a reasonable expectation of success with regard to such treatment.

10. Enablement: In my view, Dr. Davis' '318 patent would enable one of ordinary skill to practice the claimed invention. A person of ordinary skill in the art would be able to take her invention and reduce it to make and use the invention. In contrast to all of the references cited in the defendants' experts' reports, the '318 patent describes the use of galantamine to treat

AD, outlines animal tests to be carried out to confirm that utility (and progress the drug to human testing), and recommends the use of dose titration to find an appropriate dose for each patient.

III. LEVEL OF ORDINARY SKILL IN THE ART

11. In 1986, a person with ordinary skill in treating AD -- the field of the invention claimed in the '318 patent -- would have been a medical doctor treating elderly patients, that is, a physician likely to encounter patients suffering from AD. (Cummings Opening Report¶ 22)

12. It appears that Drs. Levey and Domino, in asserting that the person of ordinary skill is "a M.D. or Ph.D. interested in the field of Alzheimer's disease research" (Levey ¶ 19) mean to refer to persons actually engaged in Alzheimer's research. If so, I disagree with their description of the level of ordinary skill in the art, which I believe exaggerates the level of skill of the ordinary person.

13. At the time (that is, in 1986), the majority of doctors treating AD patients had learned little, if anything, about AD in medical school, and very few had any training or experience in the field of Alzheimer's research. Thus, the level of "ordinary" skill in the field of treating Alzheimer's patients would be a doctor whose knowledge and experience with AD would have come from encountering patients with the disease and who would have been unlikely to have had much "training and/or interest" in AD research itself.

14. For the sake of simplicity, I will use the term "AD researcher" to refer to the person used by Drs. Levey and Domino as the person of ordinary skill in the art where clarity is served by distinguishing such a person from an ordinary clinician at the time. I do not believe that the difference is significant, as it is my opinion that the '318 patent is neither anticipated nor obvious under either definition of one of ordinary skill.

IV. THE PRIOR ART SELECTED BY DRS. LEVEY AND DOMINO

15. United Kingdom Patent No. 942,200 (1960). (Levey ¶¶ 82, 103, 115-116; Domino ¶ 87) This is a patent to obtain galantamine hydrobromide from the bulbs of the Caucasian snowdrop. Further the patent indicates that the pharmacological properties of galantamine make it valuable "in the treatment of a number of diseases of the nervous system and muscles and namely — of the sequelae of poliomyelitis, radiculoneuritis, neuritis of the facial nerve, radiculitis, polyneuritis, myelitis, sequelae of injuries of the spinal cord, complications after extirpation of extramedullary tumors, sequelae after vascular diseases of the brain and after normalization, cerebral palsy and other lesions of the nervous system, myasthenia, progressive muscular atrophy, as an anticurare agent, in cases with lowered tonus of the smooth musculature of the digestive and urinary tracts, and in glaucoma as a symptomatic agent." (p. 2) Despite this long laundry-list of possible uses for galantamine, the drug is suggested neither for AD nor dementia.

16. K.G. Pernov, "Nivalin and its Curative Effect Upon Diseases of the Nervous System," Psychiatry and Neurology and Medical Psychology Bulletin on Research and Practice, 13(11) 416-420 (1961). (Levey ¶¶ 81, 83, 103, 115-116; Domino ¶¶ 37, 87) Pernov reviews the therapeutic uses of galantamine. He observes that galantamine's "therapeutic range of application above all encompasses diseases of the neuromuscular apparatus … and diseases of the peripheral motoric neuron" and is also used to treat "some diseases which affect the central motor neuron – infantile cerebral palsy, multiple sclerosis, hemiplegias subsequent insults to the brain, traumatic damage to the central nervous system." (Translation, Mylan(GAL)059584) Reviewing clinical work with galantamine, Pernov concludes that the drug "has the most favorable effect on diseases involving the peripheral motor neuron," whereas "[t]he findings from treating diseases involving the central motor neuron … are less straightforward."

(Translation, Mylan(GAL)05985-86) Pernov neither mentions AD nor suggests galantamine as a treatment for dementia.

17. P.A. Bhasker, "Medical Management of Dementia," The Antiseptic, 71:45-47 (1974) (the "Bhasker article"). (Levey ¶¶ 20, 70-72, 99-102; Domino ¶¶ 22, 63, 79-80) The Bhasker article provides a brief summary of some treatment approaches for dementia. It does not mention AD.

18. The article emphasizes the importance of promptly determining whether a demented patient is suffering from a treatable or untreatable dementia. According to the article, an exception to the usual "gloomy outlook" for dementia are cases where "one of the treatable underlying causes is detected," such as "Pellagra, B_{12} deficiency or Myxoedema." (p. 45) The article also refers to cases where "the dementing process can be arrested or reversed to a minor extent in some instances, where only a guarded prognosis can be offered. These situations include the cases of tumours (when removable), infections (like GPI) when they can be 'successfully' arrested, post-traumatic dementias, and low pressure hydrocephalus." (Id.)

19. The Bhasker article contrasts such "reversible" or treatable dementias with irreversible ones: "The irreversible cases belong to the category of dementias where there is a progressive fall-out of neurons and the course of the illness is rapidly downhill." (Id.) Based on this distinction between the reversible, treatable dementias and those that are irreversible, the article emphasizes the importance of prompt and thorough diagnosis: "Therefore, the importance of a thorough diagnosis even at the first instance must be realised, because the compartmentalisation into treatable and untreatable dementias has to be made with the utmost care." (Id.)

20. The Bhasker article describes progressive dementia as untreatable: "With regard to progressive dementia, there appears very little to offer. Only management and no treatment is possible." (Id.)

21. The Bhasker article's only reference to galantamine is in connection with reporting Luria's work in treating "local brain damage." Specifically, the article states that:

> The restoration of higher cortical functions is difficult and was once considered ...impossible; but it has lately gained importance. Luria and his colleagues have dealt with this problem in great detail. They have suggested measures of improving the higher functions in cases of local brain damage like tumour, head injury, infarct etc, by deinhibitory procedures and re-education of the rest of the brain. Deinhibition refers to the facilitation of acetylcholine activity by giving small daily doses of Cholinesterase inhibitors (Neostigmine, Gallanthamine etc.). (p. 46)

22. I agree with Dr. Levey that Bhasker's reference to "Luria and his colleagues" is a reference to the Soviet neurologist, Dr. Alexander Luria. (Levey ¶ 72) The Bhasker article does not specifically reference any Luria publication, and it is a matter of speculation what Dr. Bhasker had in mind. However, Dr. Luria's work principally related to the study of aphasia and other disorders in individuals suffering from local brain injury. The Luria publication Dr. Levey cites – Luria et al., "Restoration of higher cortical function following local brain damage," in Vincken, P.J., and Bruyn, G.W., eds., Handbook of Clinical Neurology, vol. 3, 368-433 (1969) – concerns (as its title indicates), the treatment of local brain damage. (Levey ¶¶ 72-73) There is no discussion of AD.

23. So far as I am aware, Dr. Luria never studied the treatment of AD and his work has not been cited as proposing a treatment for that disorder. It is interesting to note that, in his well-known 1985 book "The Man Who Mistook His Wife For A Hat," Dr. Oliver Sacks reports on a correspondence he had with Dr. Luria about one of his (Sack's) patients who was suffering

from a total loss of recent memory (as a result, in that case, of Korsakov's amnesia), in which Luria describes the condition as untreatable, from a clinical standpoint:

> What could we do? What should we do? "There are no prescriptions," Luria wrote, "in a case like this. Do whatever your ingenuity and your heart suggest. There is little or no hope of any recovery in his memory." (Oliver Sacks, The Man Who Mistook his Wife for a Hat: and Other Clinical Tales, p. 34 (1985))

24. Dr. Levey quotes Dr. Luria's suggestion that "pharmacological 'deblocking' therapy can reactivate **temporarily inhibited cells** and thereby contribute to the successful restoration of brain functions." (Levey ¶ 72 (emphasis added)) AD and other organic brain disorders causing dementia do not involve "temporarily inhibited cells" but rather cell death and irreversible loss of neurological function. As indicated in the quote from Dr. Sacks, above, even Dr. Luria appears to have viewed such dementia as untreatable.

25. A. Baraka, et al., "Reversal of Central Anticholinergic Syndrome by Galanthamine," Journal of American Medical Association 238:2293-2294 (1977). (Levey ¶¶ 77, 115; Domino ¶ 89) This article reports on a study in 10 healthy volunteers of the use of intravenous galantamine hydrobromide to reverse the central effects of intravenous scopolamine. There is no discussion of AD or dementia.

26. D.A. Cozanitis, "Galanthamine Hydrobromide, a Longer Acting Anticholinesterase Drug, in the Treatment of the Central Effects of Scopolamine (Hyoscine)," The Anesthetist 26, 649-650 (1977). (Levey ¶¶ 75, 103, 115-116) This brief article discusses the use of galantamine in the treatment of the central effects of scopolamine intoxication, which is described as including "clinical features such as hallucinations, delirium and coma." (p. 649) Galantamine is described as longer acting than physostigmine in connection with the management of the central effects of overdoses of anticholinergic drugs. There is no discussion of AD or of any other dementia.

27. D.A. Cozanitis, "L'hydrobromide de Galanthamine: Unsubstitute du Sulfate D'eserine (Physostigmine) pour le Traitement des Effects Cerebraux dex Substances Anti-Cholinergiques," La Nouvelle Presse Médicale., 7(45):4152 (1978). (Domino ¶ 88) This short letter notes that physostigmine's use in reversing the effects of anticholinergic drugs such as scopolamine suffers from physostigmine's short duration of action and suggests that galantamine hydrobromide may have advantages over physostigmine in this use, given galantamine's longer duration of action. There is no discussion of AD or dementia.

28. D. Daskalov, et al., "Nivalin Application and Rehabilitation Treatment of Cerebral Diseases with Aphasic Syndromes," MBI Medico-Biologic Information, 3:9-11 (1980). (Levey ¶¶ 56, 59, 79, 103, 109-111, 118; Domino ¶ 92) The article reports on the use of Nivalin (galantamine hydrobromide) in the treatment of 23 patients with brain lesions and aphasic syndromes. There is no discussion of AD or dementia.

29. R. Mohs, et al., "Studies of Cholinergic Drug Effects on Cognition in Normal Subjects and Patients with Alzheimer's Disease," Aging 17:225-230 (1981). (Domino ¶ 42) The authors review the studies of cholinergic drugs in connection with possible approaches to treating AD. The authors review a cholinesterase inhibitor approach and warn that "[t]he difficulty with this strategy is that no safe long-acting cholinesterase inhibitor is available at the present time." (p. 226-227)

30. The authors also express skepticism of relying upon a scopolamine model for drug development, which they note involves a chemically-induced blockade of cholinergic receptors. As they point out, "we know of no disease in which memory is impaired due to cholinergic blockade. Alzheimer's disease appears to affect primarily the presynaptic functions of cholinergic neurons and affects receptors only to a lesser extent." (p. 229)

31. The article concludes with a note of caution: "At present it is not clear whether studies of cholinergic drugs will lead to useful treatments for any of the debilitating dementias that afflict so many people." (p. 229)

32. W.K. Summers, et al., "Use of THA in Treatment of Alzheimer-Like Dementia: Pilot Study in 12 Patients," Biological Psychiatry, 16:145-153 (1981). (Levey ¶¶ 36, 114; Domino ¶ 42) This article reports on an unblinded, non-placebo controlled trial of the cholinesterase inhibitor THA in 12 Alzheimer's patients. The trial appeared to show some improvement in some of the patients, though, as the authors note, the study suffered from several design flaws. (pp. 152-53)

33. J.T. Coyle, et al., "Alzheimer's Disease: A Disorder of Cortical Cholinergic Innervation," Science 219: 1184-1990 (1983). (Levey ¶ 31, Domino ¶¶ 31-32) This article reviews the state of Alzheimer's research at the time, particularly with reference to the cholinergic deficit hypothesis. The authors observe that the brains of AD patients showed loss of nerve cells, and neurochemical studies indicated that presynaptic cholinergic markers are reduced in the cerebral cortex and hippocampus of affected individuals, as was activity of the acetylcholinesterase enzyme. By contrast, "muscarinic cholinergic receptors, which are concentrated on neurons receiving cholinergic innervation, have generally not been found to be decreased in the cortex of the patient with AD." (p. 1185)

34. The article compares AD to Parkinson's Disease, which is characterized by a deficiency in dopamine and may be treated with the dopamine precursor, L-dopa. The authors suggest, by way of analogy, that pharmacologic strategies for AD include administration of acetylcholine precursors, cholinesterase inhibitors, or drugs that "directly stimulate the post-synaptic muscarinic receptor." (p. 1188) Reviewing the literature, however, the authors conclude

that "[t]hus far, the results have been rather inconclusive although a few reports indicate that some patients, primarily in the early stages of AD, may experience modest improvements in cognitive functions." (p. 1189) They attribute the lack of response in AD treatment as compared with treatment of Parkinsonism to "important differences in the synaptic organization and physiology of the two affected neuronal systems." (p. 1189)

35. K. Davis, et al., "Oral Physostigmine in Alzheimer's Disease," Psychopharmacology Bulletin 19(3):451-53 (1983). (Levey ¶ 83, Domino ¶¶ 41-42) This short article reports on a 13-patient trial of oral physostigmine involving both dose finding and replication stages. The trial was also divided into two parts, the first involving 4 patients and the second 9, with the second part involving the more reproducible ADAS scale being used to rate the patients. For those 9, the article reports that only two patients showed improvements judged "clinically meaningful" and states that "[t]he heterogeneity of response to physostigmine or any cholinesterase inhibitor is not unanticipated." (pp. 451-52) The authors hypothesize that "[t]he efficacy of physostigmine is a function of the integrity of the cholinergic neuron and its ability to synthesize acetylcholine" and also that patient's response may depend upon "the extent that neurotransmitters other than acetylcholine are involved in a particular patient's dementia." (p. 452) A noradrenergic deficit is proposed as "the most obvious example" of a confounding problem in Alzheimer's patients. (Id.)

36. B.S. Greenwald, et al., "Perspectives - Neurotransmitter Deficits in Alzheimer's Disease. Criteria for Significance, Journal of American Geriatrics Society, 31: 310-316 (1983). (Levey ¶¶ 31-32, 80, 102-103, 113, 116; Domino ¶ 84) This article reviews the evidence supporting the cholinergic deficit hypothesis in AD and the attempts at pharmacologic enhancement of the cholinergic system. The authors conclude:

> [W]hile it is generally agreed that L-dopa and other agonists can ameliorate symptoms in PD [Parkinson's Disease] patients, the effects of cholinergic-enhancing compounds in AD are much more limited. Encouragingly, positive effects of cholinomimetics have been reported; **however, a level of clinical utility has not been achieved**. Possible explanations for this differential effect by DA [dopamine] and ACh [acetylcholine] agonists in PD and AD, respectively, are these: (a) cholinergic neurons are regulated differently than are dopaminergic neurons, (b) neurochemical deficits are more complex in AD than in PD, and (c) **currently available cholinergic agents are unable to substantially influence symptoms of AD**. (p. 313 (emphasis added))

37. C. Johns, et al., "The Cholinergic Treatment Strategy in Aging and Senile Dementia," Psychopharmacology Bulletin, 19(2): 185-197 (1983). (Domino ¶¶ 35, 85). This article reviews the role of the cholinergic hypothesis in treatment strategies for AD, including possible uses of acetylcholine precursor therapy in connection with metabolic enhancers such as piracetam, guanidine, or 4-amino-pyridine (p. 188), the cholinesterase inhibitors physostigmine and THA (pp.. 189-92), and the muscarinic receptor agonists arecoline and oxotremorine. (p. 187, 192)

38. With regard to the cholinesterase inhibitors, the authors note that the "only currently available relatively safe pharmacologic agents of this type are physostigmine, which produces chronic enhancement of the cholinergic system by competitively inhibiting acetylcholinesterase, and tetrahydroaminoacridine (THA), a centrally-acting reversible acetylcholinesterase inhibitor with a longer half-life than physostigmine." (p. 189) The authors observe that "the variability of these results [with physostigmine], both in terms of overall efficacy and specific areas of improvement, has generated debate over the clinical utility of cholinesterase inhibitor therapies." (Id.) They observe that the practical clinical utility of the drugs remains uncertain. (pp. 191-92)

39. The article is more encouraging about agonists than cholinesterase inhibitors. The authors note that, while cholinesterase inhibitors show more promise that precursor therapy:

> Both strategies, however, share a fundamental limitation in that they are dependent on an intact presynaptic neuron to provide a substrate for their activity. These problems may be circumvented by administering cholinergic agents which work directly at postsynaptic receptor sites, since the number of postsynaptic muscarinic binding sites is not reduced in SDAT patients as compared to age-matched controls. (p. 192)

The authors review encouraging results with the agonist arecoline and suggest that "[o]xotremorine, a longer-acting muscarinic agent, may be a more ideal compound, and clinical confirmation of its usefulness in SDAT awaits therapeutic trials." (Id.)

40. The authors conclude with a note of caution, observing that "[t]he success of cholinomimetic treatment strategies thus far has been modest, and definitive treatment of SDAT awaits clarification of complex neurochemical variables, delineation of parameters that can predict response, and development of appropriate safe, long-acting pharmacologic agents." (p. 193)

41. L.I. Thal, et al., "Memory Enhancement with Oral Physostigmine in Alzheimer's Disease," The New England Journal of Medicine 308(12):720-1(1983). (Levey ¶¶ 74, 114; Domino ¶ 83) This letter to The New England Journal of Medicine describes a study of memory enhancement with a combination of oral physostigmine and lecithin (an acetylcholine precursor) in 12 patients diagnosed with early AD. According to the article, oral physostigmine was used because "parenteral physostigmine is not suitable for long-term therapy." (p. 720) Memory was tested using a "12-item, 12-trial selective reminding task." Eight of the 12 patients showed improvement on the task, and the authors conclude:

> Orally administered physostigmine appears to be absorbed from the gut; the optimal drug dose is about 2.5 mg. Such drugs, which are potent and specific enhancers of the cholinergic system,

> may prove to be clinically useful in the treatment of Alzheimer's disease. (p. 720)

42. K. Rathmann, et al., "Alzheimer's Disease Clinical Features, Pathogenesis, and Treatment," Drug Intelligence and Clinical Pharmacology, 18:684-91 (1984). (Levey ¶¶ 78, 102-103; Domino ¶ 86) This article reviews the clinical features of AD and the approaches to treatment as of that date. The authors note that:

> [t]hree types of pharmacologic agents have been used to stimulate cholinergic activity: (1) agents that increase acetylcholine production in the presynaptic neuron (acetylcholine precursors); (2) agents that inhibit the breakdown of acetylcholine (cholinesterase inhibitors), and (3) agents that directly stimulate postsynaptic cholinergic receptors (cholinomimetic agents). Other agents that have been investigated include naloxone, vasopressin analogs, ergot alkaloids, and amphetamines. (p. 687)

43. With regard to precursor therapy, the authors observe that while there have been some positive results with high-dose lecithin, most studies show little or no benefit in memory enhancement from precursor therapy. The authors suggest that "[e]xtensive loss of cholinergic neurons capable of increasing acetylcholine production and/or the inability of these agents to facilitate the release of acetylcholine into the synaptic space may contribute to their ineffectiveness." (p. 688)

44. With regard to cholinesterase inhibitors, the authors note that "[t]he limitation of this approach, like that of acetylcholine precursor therapy, is the availability of intact cholinergic neurons to synthesize acetylcholine." (Id.) The authors review a number of studies involving physostigmine and conclude: "Clearly, controlled studies evaluating long-term treatment are required to determine the clinical usefulness of acetylcholinesterase inhibitors in Alzheimer's disease ...." (Id.)

45. Concerning physostigmine, the authors observe that it has "limited usefulness due to its very short duration of action (<1 h) and the high incidence of peripheral cholinergic side effects. However, it has served as a useful pharmacological model." (Id.)

46. With regard to agonists, the authors note that a small study of arecoline showed improvement in cognitive function but caution that that drug too "has a very short duration of action and a high incidence of side effects, which limit its usefulness." (Id.)

47. The authors also review other, non-cholinergic treatment attempts, such as with naloxone, vasopressin, metabolic enhancers, amphetamines, valproic acid, and carbamazepine, for some of which encouraging studies existed. For example, the authors describe encouraging reports from early studies on the opioid antagonist naloxone and suggest that "[s]hould further investigations support the efficacy of narcotic antagonists, naltrexone may be an ideal agent for chronic use in patients with Alzheimer's disease, due to its simplicity of administration and negligible toxicity." (p. 689)

48. The authors conclude that:

> there has been wide-spread interest in pharmacologic agents to enhance cholinergic function. Despite encouraging results with physostigmine, **the clinical importance and usefulness of this class of agents remain undetermined**. Other drug prototypes, such as naloxone and neural metabolic enhancers show some potential in preliminary studies and require further study. (p. 689 (emphasis added))

49. V. Hartounian, et al., "Cholinergic Modulation of Memory in Rats," Psychopharmacology 87(3):266-271 (1985). (Levey ¶¶ 32, 83) This article reports a study of various cholinergic agents on healthy rats. The article reports that both the presynaptic cholinergic agents 4-Amino-pyridine and physostigmine and the post-synaptic agents arecoline and oxotremorine enhanced retention of learned responses in rats at low doses and impedes retention at high doses. The article also notes that the effects of all of the drugs studied (with the

exception of 4-AP but including physostigmine) have been investigated under other conditions, with conflicting results: "with some authors finding potentiation of learning and memory, others reporting disruption of memory processes, and still others finding no significant effects." (p.269)

50. R. Mohs, et al., "Clinical Studies of the Cholinergic Deficit in Alzheimer's Disease." Journal of the American Geriatrics Society 33(11): 749-757 (1985). (Levey ¶ 83; Domino ¶¶ 41). This paper (which lists Dr. Bonnie Davis as a co-author) reports on studies of intravenous and oral physostigmine in 16 and 12 patients, respectively. The study on intravenous physostigmine saw some memory enhancement in most patients, but were unable to correlate improvement with any "clinical variable." The study of oral physostigmine saw improvement in roughly half of the patients. The authors acknowledge that, in light of recent work, "the search for any reasonably effective pharmacologic treatment must address several different problems if it is to succeed." (p. 755) The problems identified in the article include difficulties in diagnosis, the presence of neurochemical deficits other than acetylcholine in Alzheimer's patients, and the difficultly in determining whether a cholinomimetic drug is in fact improving a patient's cholinergic activity.

51. The article ends on a discouraging note:

> Combining careful biologic assessment and clinical diagnosis with attention to the unique pharmacologic properties of cholinergic drugs may ultimately identify a group of AD/SDAT patients who can derive meaningful clinical benefit from cholinesterase inhibitors or cholinergic agonists. However, it must be recognized that even when these conditions are met, the use of such drugs could be severely limited. It has been pointed out, for example, that cholinergic cells have relatively few postsynaptic projections that are also nonoverlapping, so that it is difficult for surviving cholinergic cells to compensate functionally for lost cells by increasing their firing rate. In addition, none of these drugs may be able to duplicate the phasic action of cholinergic cells in transmitting information. If such considerations prove to be true then any pharmacotherapy of AD/SDAT may have to depend upon

> manipulation of transmitters and cotransmitters operating at sites postsynaptic to the dying neurons. (p. 756)

52. Mohs et al., "Oral Physostigmine Treatment of Patients with Alzheimer's Disease The American Journal of Psychiatry, 142(1):28-33 (1985). (Levey ¶¶ 76, 102-103, 113, 116; Domino ¶¶ 41, 59) The article (which includes Dr. Bonnie Davis as a co-author) reports on a 12-patient trial of oral physostigmine on AD patients. The trial was divided into dose finding and replication stages, and the effect of physostigmine on AD symptoms was measured with the Alzheimer's Disease Assessment Scale ("ADAS").

53. The article explains the selection of physostigmine as the best available agent for improving the central cholinergic function of Alzheimer's patients:

> From a psychopharmacologic perspective one of the difficulties involved in testing the therapeutic implications of the cholinergic deficit in Alzheimer's disease is that few of the available cholinomimetic drugs are good candidates for clinical trials.... Available long-acting cholinesterase inhibitors and cholinergic agonists such as isoflurophate and oxotremorine, respectively, are drugs with potentially serious side effects that limit their utility as therapeutic agents. **Of the remaining cholinomimetics, physostigmine appears to be the most viable candidate for clinical trials at present**. (p. 28 (emphasis added))

54. Of the 10 patients who appeared to benefit from physostigmine in the dose finding stage and who completed the replication stage, three did not improve on physostigmine in the replication phase, four improved only slightly (less than 10% on the ADAS scale), and three improved more substantially (greater than 10% on the ADAS scale). (p. 31)

55. The authors observe that "[f]rom a clinical perspective these results can be viewed in two ways. On the one hand, oral physostigmine produced a consistent and clinically evident improvement in symptoms for only about 30% of patients. Thus it is clear that physostigmine, in the doses used in this study, does not have therapeutic benefits comparable to those seen with L-dopa in Parkinson's disease or with neuroleptics in schizophrenia. On the other hand, it appears

that physostigmine does produce a meaningful reduction in symptom severity in at least some patients with Alzheimer's disease." (p. 31)

56. The authors observe that the results of their trial were consistent with prior studies, some of which reported positive results and others negative. They postulate several explanations for the inconsistent results, including the possibilities that (1) some of the patients were misdiagnosed, (2) some of the patients had significant neurotransmitter deficits that could not be corrected by physostigmine, and (3) physostigmine may have failed to improve central cholinergic activity in some of the patients. (pp. 31-32)

57. The authors conclude that:

> [t]here are at least two implications for these results for future research on the pharmacotherapy of Alzheimer's disease. First, they suggest that drugs which increase cholinergic activity are likely to be of benefit to some patients with Alzheimer's disease. This in turn implies that additional effort is needed to develop safer and more long-acting drugs which increase cholinergic activity, either by directly affecting receptors, by inhibiting cholinesterase, or by stimulating presynaptic activity. A second implication is that efforts should be made to identify those individuals likely to benefit from treatment with oral physostigmine... It may be, then, that age at onset or some other clinical parameter will predict responsivity to purely cholinergic treatments. However, large studies must be conducted to determine whether this speculation is correct. (p. 32)

58. Dr. Levey also cites a long list of articles as purportedly providing "further support" for his contentions, but he does not describe the contents or relevance of these articles. (Levey ¶ 83) In brief, the additional citations are as follows:

59. C.M. Smith and M. Swash, "Physostigmine in Alzheimer's Disease," The Lancet 1:42 (1979). This short letter to The Lancet reported on a small study of intravenous physostigmine using a variety of memory tests. The authors report that physostigmine appeared to improve name recall but none of the other memory tests.

60. M.I. Levy, et al., "Research Subject Recruitment for Gerontological Studies of Pharmacological Agents," Neurobiology of Aging, 3(1): 77-79 (1982). This article discusses the authors "experience in recruiting patients for a study of cholinomimetic agents in Alzheimer's Disease." (p. 77) The article describes difficulties with recruitment, diagnosis, and testing of patients, and the authors characterize the implications of their experience as "disquieting," with potential problems with recruitment, sample size, and diagnosis raising issues with interpretation of study results. (p. 78)

61. VA Krauz et al., "Role of Cholinergic Mechanism in ATFase Activity and Glycolysis Intensity Regulation in the Rat Neocortex, Hippocampus and Truncus Cerebri, Farmakologia I Toksikologia, 1:22-26 (1982) (Translation, TEV-G004477-4482). This article reports on a study of the influence of galantamine (and other drugs) on the neurochemistry of rats. Rats were injected with galantamine, metamysil, and eterofen and then decapitated 40 minutes later to examine the brain. The results indicated that cholinergic mechanisms may help regulate the NA, K-ATFase activity in the brain, which is thought to be associated with brain excitability level and may impact the process of learning and memory. The clinical significance of the authors' observations is uncertain.

62. A. Plaitakis, et al., "Homer's Moly Identified as Galanthus Nivalis L: Physiologic Antidote to Stramonium Poisoning," Clinical Neuropharmacology 6(1): 1-5 (1983). The authors, reflecting on Homer's Odyssey, argue that galantamine, derived from natural sources, is a possible source of the antidote to a drug that induced delirium in Odysseus' men and caused them to cannibalize each other. The article notes the snowdrop (galanthus nivalis) matches the description Homer gave of the antidote drug moly. Furthermore, the description of the antidote's

location corresponds to where the snowdrop grows. Cannibalism is uncommon, if not unknown, in AD.

63. M. Bretagne, et al., "Essais Cliniques en Anesthésiologie D'un Nouvel Anticholinestérasique la Galanthamine," Anesthesie Analgesie Reanimation, 1:285-92 (1965) (Translation, JAN RAZ 134055-61) This article reports on the curare inhibition effects of galantamine by administering it to 50 patients undergoing a wide variety of surgical procedures. The authors find galantamine effective for this purpose, though also note that "the activity of Galanthamine is relatively weak compared with that of neostigmine and [physostigmine]." (JAN RAZ 0134058). The article also observes that "the action of this product [galantamine] persists for over two hours." (JAN RAZ 0134061)

64. D.A. Cozanitis, et al., "A Comparative Study of Galanthamine Hydrobromide and Atropine/Neostigmine in Conscious Volunteers," Anaesthesist, 416-21 (1971). The article reports on a study of two groups of 10 volunteers comparing the effects of galantamine to a combination of neostigmine and atropine. The article observes that "[t]hree factors must be borne in mind when comparing the 2 anticholinesterase drugs used in this study. First, the central action of galanthamine, second, the fact that neostigmine .... is 20 times more potent, and third, that due to the very slight muscarinic effect of galanthamine, no atropinization is necessary." (p. 420)

65. K. Davis, et al., "Physostigmine: Improvement of Long-Term Memory Processes in Normal Humans," Science, 201(4352):272-74 (1978). This article reports on the intravenous administration of physostigmine to 19 healthy male subjects. The authors report some improvements in long-term memory with physostigmine, but note that there was "considerable

variability between subjects" and that the "[f]actors that are predictive of a physostigmine-induced improvement in LTM are not readily apparent." (p. 273)

66. K. Davis and R. Mohs, "Enhancement of Memory Processes in Alzheimer's Disease with Multiple-Dose Intravenous Physostigmine," The American Journal of Psychiatry, 139(11): 1421-24 (1982). Davis and Mohs administered physostigmine intravenously to patients with AD. The authors report that "[l]ow doses of intravenous physostigmine transiently improved the ability of patients with Alzheimer's disease to store information into long-term memory" but cautions that "until there is long-term administration of cholinomimetic agents to patients with Alzheimer's disease, it will be impossible to judge their ultimate clinical utility." (p. 1423)

67. B.H. Peters, et al., "Effects of Physostigmine and Lecithin on Memory in Alzheimer's Disease," Annals of Neurology 6(3): 219-21 (1979). This article reports on a study in which lecithin (a precursor), physostigmine or lecithin plus physostigmine were tested in 5 Alzheimer's patients. The authors find that "[w]hile neither physostigmine nor lecithin alone consistently improved long-term memory processes, their combined action augmented LTS, LTR, or both, in each of the patients tested under this condition." (p. 221) The authors also note that "[p]hysostigmine and lecithin had no obvious effect on general cognitive efficiency or social functioning during the brief course of this study" and warn that "[t]hese data are insufficient to warrant the use of lecithin with physostigmine as a clinical regimen." (p. 220-21)

V. ANTICIPATION

68. I disagree with the assertions of Drs. Levey and Domino that the Bhasker article anticipates the claims of the '318 patent. In my opinion, a person of ordinary skill reading the Bhasker article in 1986 (or, for that matter, at any time), would not understand the article to be suggesting galantamine for the treatment of AD. To the contrary, as I will discuss, the reader

would instead understand that article to be saying that "progressive" dementia (which is the closest the Bhasker article comes to referencing AD at all) is untreatable.

69. The article's single reference to galantamine comes in its entirely unrelated discussion of "deinhibitory" treatment measures for "local brain damage." Specifically, the Bhasker article states that Luria and his colleagues "have suggested measures of improving the higher functions **in cases of local brain damage like tumour, head injury, infarct etc.**, by deinhibitory procedures and re-education of the rest of the brain. Deinhibition refers to the facilitation of acetylcholine activity by small daily doses of Cholinesterase inhibitors (Neostigmine, Gallanthamine etc.)." (Bhasker p. 46 (emphasis added)) Alzheimer's disease is not a type of local brain damage, and it is not analogous to "tumour, head injury, or infarct." A person of skill in the art would not read the reference to local brain damage in the Bhasker article as encompassing AD.

70. Drs. Levey and Domino appear to assert that the Bhasker article's reference to "progressive dementia" would be understood to encompass AD. (Levey ¶ 99; Domino ¶ 79) As discussed below, I think this is doubtful or at least speculative as well. But for present purposes, that does not matter, for the Bhasker article does not suggest galantamine as a treatment for "progressive dementia." Quite the reverse: the article expressly states that progressive dementias are untreatable — "With regard to progressive dementia, there appears very little to offer. Only management and no treatment is possible." (Bhasker p. 45)

71. Moreover, the Bhasker article puts great emphasis on "thorough diagnosis" of dementias so as to distinguish between the "treatable" and "untreatable" ones. This would further underscore the distinction drawn in the article between "progressive dementia," which

Bhasker puts in the "untreatable" category, and "local brain damage," for which galantamine (and neostigmine) is suggested.

72. Moreover, the fact that Bhasker lumps galantamine with neostigmine as agents for "deinhibition" would further confirm to a person of ordinary skill that Bhasker is not describing therapy for a dementia such as AD. Neostigmine is not centrally acting, as a person of ordinary skill would know. Cozanitis (1977) points out, for example, that: "Having a quaternary ammonium group, it [neostigmine] cannot penetrate the blood-brain barrier and is therefore useless in combating the central effects of anticholinergic drugs." (p. 650)

73. In addition, I believe that it is far from clear that a person of ordinary skill would understand the Bhasker article to be referencing AD at all. The article never mentions AD by name. Drs. Levey and Domino assert that one of ordinary skill would understand the article to encompass AD in its description of "irreversible cases belong[ing] to the category of dementias where there is a progressive fall-out of neurons and the course of the illness is rapidly downhill." (Bhasker p. 45) (Levey ¶ 99, Domino ¶ 79) But AD is not characterized by a rapid, downhill course. Instead, while the progression of AD is steady, it is also typically slow – with patients often living 10 years or more after first diagnosis. A person of ordinary skill would not view the course of an Alzheimer's patient as proceeding "rapidly downhill."

74. It is my opinion that a person of ordinary skill reading the Bhasker article would recognize that in 1974, when the article was published, the prevalence of AD was only just beginning to be understood; many still viewed the disease as a rare disorder of middle-age, and the disease was rarely studied or discussed in the literature. With that context, a reader would likely understand the article as having nothing to say about AD.

75. In addition, I do not believe that the Bhasker article would have taught anything – let alone anything about AD – to a person of ordinary skill interested in either AD or galantamine in 1986, because he or she would never have found the article.

76. It is my understanding that, as of 1986, the Bhasker article had neither been indexed nor cited by any other publication; nor is it a reference that would have been generally reviewed in its own right. At the time, the standard index was the Index Medicus, which was published by the National Library of Medicine ("NLM"). (The Index Medicus has since been replaced by MEDLINE, a computerized index). Index Medicus was a monthly guide to articles contained in approximately 4,000 journals. Antiseptic was not included by the NLM in the Index Medicus.

77. I understand that the defendants have noted that various libraries have copies of The Antiseptic journal in which the Bhasker article appears. However, the mere maintenance of a copy of a journal in a library does not make the contents of the journal accessible to clinicians or researchers. Unless it was indexed or cited in a reference that is reviewed, a person of ordinary skill would not have been able to locate this article through a reasonably diligent search. The fact that an article exists somewhere does not make it accessible unless there is a way of finding it. For example, I have done extensive reading in the field of neurology generally, and AD specifically, and I had never seen or heard of the Bhasker article, or of the journal Antiseptic, until this litigation. In my opinion, that article was simply not publicly accessible.

VI. NON-OBVIOUSNESS

A. Differences between the prior art and the claimed invention

78. I reviewed the subject matter of the '318 patent in my opening report. (See, e.g., Cummings ¶¶ 55-60) There are at least two differences between the patented invention and the

prior art as of January 1986: (1) the prior art did not describe any drug as therapeutically effective for the treatment of AD; and (2) the prior art did not even suggest galantamine (or its salts) as a treatment for AD, let alone describe it as a therapeutically effective treatment.

79. As to the first difference, Drs. Levey and Domino assert that the then-published studies on physostigmine and tacrine showed those drugs to be therapeutically effective treatments for AD. Dr. Levey, for example, cites several articles by Drs. Mohs and Ken Davis as disclosing physostigmine as therapeutically effective. (Levey ¶ 116) But a review of those articles refutes this assertion.

80. Mohs and Davis, "Choline Chloride Effects on Memory: Correlation with the Effects of Physostigmine," Psychiatry Research 2(2): 149-56 (1980), cited at Levey ¶¶ 31-32, 113-114, 116, did not study Alzheimer's patients at all, and the article's focus, as the name makes clear, was on choline chloride, an acetylcholine precursor. In any event, the article is not encouraging for cholinergic enhancement of memory, since it concludes that "the cognitive changes produced by choline are small even in those subjects who appear responsive, and, thus, it is questionable whether these changes could be of any practical significance." (p. 154)

81. B.S. Greenwald, et al., "Neurotransmitter Deficits in Alzheimer's Disease: Criteria for Significance," Journal of the American Geriatrics Society, 31(5):310-16 (1983), cited at Levey ¶ 31-32, 80, 102-3, 113, 116 and Domino ¶ 84, reviews the work on cholinesterase inhibitors and other cholinergic enhancement approaches and expressly acknowledges that clinical utility had not been shown. This is plain from their conclusion:

> While it is generally agreed that L-dopa and other agonists can ameliorate symptoms in PD patients, the effects of cholinergic-enhancing compounds in AD are much more limited. Encouragingly, positive effects of cholinomimetics have been reported; **however, a level of clinical utility has not been achieved**. Possible explanations for this differential effect by DA

> and ACh agonists in PD and AD, respectively, are these: (a) cholinergic neurons are regulated differently than are dopaminergic neurons, (b) neurochemical deficits are more complex in AD than in PD, and (c) **currently available cholinergic agents are unable to substantially influence symptoms of AD**. (p. 313 (emphasis added))

82. V. Haroutunian, et al., "Cholinergic Modulation of Memory in Rats, Psychopharmacology, 87(3):266-71 (1985), cited at Levey ¶¶ 32, 83, involved studies on healthy rats, not Alzheimer's patients. The article reports that both the presynaptic cholinergic agents 4-Amino-pyridine and physostigmine and the post-synaptic agents arecoline and oxotremorine enhanced retention of learned responses in rats at low doses and impedes retention at high doses. None of the compounds is described as therapeutically effective in Alzheimer's patients. The sole reference to treatment of AD is the authors' suggestion that "[i]f this generalization [about similar effects in man] should prove valid in experiments with normal human subjects, it may be possible to use these or similar cholinergic compounds in the treatment of memory disorders such as those characteristic of Alzheimer's disease." (p. 270) This highly qualified speculation, which does not distinguish cholinesterase inhibitors from agonists or precursors, would not be understood by a reader to describe any particular compound (or even a cholinergic enhancing approach generally) as in fact therapeutically effective. Also, the article's suggestion that cholinergic agents may impede retention at higher doses (a so-called "U-shaped dose response") would, to the contrary, be further discouraging in terms of clinical use.

83. C. Johns, et al., "The Cholinergic Treatment Strategy in Aging and Senile Dementia," Psychopharmacology Bulletin, 19(2):185-97 (1983), cited at Domino ¶¶ 35, 85, reviewed studies of the cholinesterase inhibitors physostigmine and THA in Alzheimer's patients. The authors acknowledge that "the variability of these results, both in terms of overall efficacy and specific areas of improvement, has generated debate over the clinical utility of

cholinesterase inhibitor therapies" (p. 189), and they observe the practical clinical utility of the drugs remains uncertain. (pp. 191-92)

84. Far from demonstrating the therapeutic effectiveness of cholinesterase inhibitors, the Johns article instead observes that those drugs (like precursors) "share a fundamental limitation in that they are dependent on an intact presynaptic neuron to provide a substrate for their activity" (p. 192) and the authors point out that this limitation may be circumvented through use of a postsynaptic muscarinic agonist. Oxotremorine is suggested as "a more ideal compound." (Id.) Finally, the article expressly rejects the proposition that clinical utility has been demonstrated for any cholinergic approach: "The success of cholinomimetic treatment strategies thus far has been modest, and definitive treatment of SDAT awaits clarification of complex neurochemical variables, delineation of parameters that can predict response, and development of appropriate safe, long-acting pharmacologic agents." (p. 193)

85. R. Mohs and K. Davis, "Interaction of Choline and Scopolamine in Human Memory," Life Sciences 37(2):193-97 (1985), cited at Levey ¶ 32, studied the effects of dietary choline on healthy volunteers who were administered scopolamine and concluded that "precursors to Ach may be of limited use in treatment strategies designed to increase cholinergic activity pharmacologically." (p. 196) Neither physostigmine nor any other cholinesterase inhibitor was studied, but the authors' review of the literature was pessimistic, observing that "[a]ttempts to enhance cholinergic transmission and memory with agonists or cholinesterase inhibitors have met with limited success." (p. 193)

86. V. Haroutunian, et al., "Pharmacological Alleviation of Cholinergic Lesion Induced Memory Deficits in Rats," Life Sciences 37(10):945-52 (1985), cited at Levey ¶ 32, studied physostigmine in nbM lesioned rats. This study, which was published in the Fall of

1985, is described as the "first demonstrations of pharmacologically reversible passive avoidance deficits in rats with bilateral excitotoxic lesions of the nbM." (p. 951) The relevance of these rat studies to Alzheimer's patients was unclear at the time, and the article does not describe physostigmine, or any other compound, as therapeutically effective for any disease. Moreover, the finding that higher doses of physostigmine were necessary for memory enhancement in lesioned rats relative to controls, which the article describes as "provocative," would have caused concerns about potential therapeutic use of cholinesterase inhibitors, given the prevailing concern with the tolerability of those compounds and their narrow therapeutic index.

87. Finally, Mohs et al., "Oral Physostigmine Treatment of Patients with Alzheimer's Disease," The American Journal of Psychiatry 142(1):28-33 (1985), cited at Levey ¶¶ 76, 102-3, 113-114, 116 and Domino ¶¶ 41, 59, studied oral physostigmine in 12 Alzheimer's patients. The article does not describe physostigmine as therapeutically effective. To the contrary, the authors observe the inconsistent results with oral physostigmine in their study and other "negative reports" about cholinomimetics elsewhere in the literature. (p. 31) The authors speculate on possible reasons for the inconsistent results of the drug and express a need for a method of identifying individuals likely to benefit from oral physostigmine – a matter requiring, in the authors' view, large clinical studies. (p. 32)

88. In short, none of the articles upon which Drs. Levey and Domino purport to rely in fact describe physostigmine or any other drug as therapeutically effective for the treatment of AD. Quite the reverse: those articles generally express reservations about the drugs and recognize the need for further study.

89. In addition, Drs. Levey and Domino have selected only a small part of the prior art literature concerning cholinergic approaches to AD. The papers Drs. Levey and Domino cite

need to be read (as a person of ordinary skill would read them) in the context of the body of failed physostigmine and tacrine clinical studies ignored by Drs. Levey and Domino:

a) In 1980, P.J. Delwaide et al. investigated whether physostigmine improved memory of Alzheimer's patients and found "[n]o effect of physostigmine ha[d] been observed." P.J. Delwaide et al., "Acute Effect of Drugs upon Memory of Patients with Senile Dementia," ACTA Psychiatrica Belgica 80:748-754, at 748 (1980).

b) In 1981, Ashford et al. provided intravenous physostigmine to six patients with AD, tested them using the modified Buschke Word List Learning test or a modified Benton Visual Retention Test and found that physostigmine "did not improve learning or memory ... in older patients who were moderately to severely demented." Ashford et al., "Physostigmine and its Effect on Six Patients," American Journal of Psychiatry 138(6):829-30, at 830 (1981).

c) In 1982, Caltagirone et al. administered physostigmine orally for one month to 8 patients with a clinical diagnosis of AD and concluded "no difference was found for the results obtained on MDB [Mental Deterioration Battery] by AD patients before and after treatment." Caltagirone et al., "Oral Administration of Chronic Physostigmine Does Not Improve Cognitive or Mnesic Performances in Alzheimer's Presenile Dementia," International Journal of Neuroscience 16:247-249, at 248 (1982).

d) In 1982, Sullivan et al. aimed to discover if physostigmine improves mnemonic capacities in patients with AD and found that "physostigmine infusion did not produce any reliable change in the performance of these patients as a unitary group." Sullivan et al., "Physostigmine and Lecithin in Alzheimer's Disease," Aging, Volume 19, 361-367, at 362 (1982).

e) In 1982, Wettstein administered a combination of lecithin and physostigmine and evaluated patients on verbal and memory tests and concluded "[n]o improvement in recent memory or other psychological functions could be demonstrated." "No Effect from Double-Blind Trial of Physostigmine and Lecithin in Alzheimer's Disease, Annals of Neurology 12:210-212, at 211 (1983).

f) In 1982, Drachman et al. gave lecithin for 5 weeks, then gave physostigmine intravenously, and then tried a combination of both treatments and evaluated the subjects using memory tests and declared that "physostigmine failed to improve performance on memory tasks..." D. Drachman, et al., "Memory Decline in the Aged: Treatment with Lecithin and Physostigmine," Neurology 32:944-950, at 949 (1982).

g) In 1982, Kaye et al. conducted a study in which tacrine was given to Alzheimer's patients and found no effect. See W. Kaye, et al., "Modest

facilitation of memory in dementia with combined lecithin and anticholinesterase treatment." Biological Psychiatry 17:275-80 (1982).

h) In 1983, Jotkowitz treated ten patients daily with mild to severe AD with oral physostigmine for up to 10 months and declared they showed "no improvement," consistent with prior clinical studies on physostigmine such as that of Dr. Wettstein. See Jotkowitz, "Lack of Clinical Efficacy of Chronic Oral Physostigmine in Alzheimer's Disease" Annals of Neurology 14:690-691, (1983) ("[T]he present study confirms the previous report of the lack of benefit of physostigmine in AD and extends the observation to long-term oral administration.").

90. The journals referenced in the preceding paragraph --Annals of Neurology, Neurology, and Biological Psychiatry --are among the most prestigious, widely cited, and widely *read journals in neurology* —in sharp contrast with Antiseptic. The Annals of Neurology, Neurology, and Biological Psychiatry are regularly reviewed by researchers and clinicians and are located on the bookshelves of virtually every academic medical library.

91. Dr. Levey asserts that "[o]nce the physostigmine trials were known, it is not an exaggeration to say that it would have been obvious to anyone reading the literature that the ideal drug candidate for treating Alzheimer's disease would perform like physostigmine, but without the drawbacks." (Levey ¶ 36) Dr. Levey does not cite any publication which actually draws this conclusion. The truth was, in fact, precisely to the contrary. As I discussed in my opening report, there was considerable skepticism in the art regarding the treatment of AD with a cholinesterase inhibitor, and many preferred alternative approaches, such as metabolic enhancers, muscarinic receptor agonists, or hormone therapy. In my opinion, it was clearly not obvious at the time that a cholinesterase inhibitor would be therapeutically effective in treating AD.

92. Dr. Levey's assertion is contradicted by contemporaneous reviews of the physostigmine and tacrine literature that were published at the time. For example, in a 1986 review, Raymond Bartus and his coauthors reviewed the physostigmine literature and found that

"[a]lthough positive effects have been obtained in both aged humans and nonhuman primates with memory impairments, the effects are quite subtle and require strictly controlled test conditions and special attention to large individual variations in the most effective dose." R.T. Bartus, et al., "Cholinergic Treatment for Age-Related Memory Disturbances: Dead or Barely Coming of Age?" in T. Crook, et al., eds., Treatment Development Strategies for Alzheimer's Disease 421-450 (1986). Bartus and his co-authors expressly rejected precisely the conclusion that Dr. Levey now says was obvious, namely that the therapeutic efficacy of cholinesterase inhibitors was obvious: "Whatever the positive results that have been claimed or obtained with cholinergic agents, one must recognize that they are extremely subtle, quite variable, **and offer little or no significant therapeutic relief in activities of daily living**." (p. 428 (emphasis added)) The authors' conclusion at the time was that "we are probably a long way from achieving an effective treatment for the symptomatic loss of cognitive function in senescent or demented patients." (p. 441) To similar effect is Bartus' 1985 review of the literature, Bartus et al., "Cholinergic Hypothesis: A Historical Overview, Current Perspective, and Future Direction," in Olton, et al., eds., Memory Dysfunctions: An Integration of Animal and Human Research from Preclinical and Clinical Perspectives Annals of the New York Academy of Sciences, 444:332-58 (May 30, 1985).

93. Another example is a 1984 review by Kaye Rathmann and Christopher Conner, which Drs. Levey and Domino themselves cite. (Levey ¶¶ 78, 102-103; Domino ¶ 86) K. Rathmann and C. Conner, "Alzheimer's Disease Clinical Features, Pathogenesis, and Treatment," Drug Intelligence and Clinical Pharmacology 18:684-91 (1984). After reviewing the work on cholinesterase inhibitors (and other attempts at treatment), the authors conclude that "[d]espite encouraging results with physostigmine, the clinical importance and usefulness of this

class of agents remain undetermined." (p. 689) There are plenty of other examples. See, e.g., L. Berg, "Aging and Dementia" in A. Pearlman and R. Collins, eds., Neurological Pathophysiology 250-273(1984):

> There have been inconsistencies in the findings from various laboratories in experiments testing the cholinergic hypothesis. Responses of patients with AD to cholinomimetic drugs and other agents to promote cholinergic transmitter function have been spotty and disappointing. Should the cholinergic system deficiency prove to be important in AD, one would still have to deal with the question of what causes the loss of cholinergic neurons. Is there a critical decline in trophic factors essential for healthy cholinergic neurons? If so, what leads to that decline? Do cholinergic deficiencies result from the same factors that give rise to plaques or tangles or loss of cortical neurons? Of course, there is the possibility that the cholinergic defects are secondary rather than primary in AD. (p. 270-271)

94. Moreover, as one of ordinary skill would have recognized, even the sometimes encouraging results on physostigmine and tacrine were confined to narrow and artificial measures of memory. Improvements in such tests are not sufficient to address therapeutic efficacy, which requires clinically meaningful improvements. Put simply, improving an Alzheimer's patient's performance on an ADAS-cog test, for example, is not by itself treatment of the disease. To constitute treatment, the therapy must result in clinical benefits, not just improvements in test scores.

95. This point was made expressly by FDA in its "Guidelines for the Clinical Evaluation of Antidementia Drugs", which were published in 1990. To gain approval by the FDA for an indication to treat a dementia such as AD, the sponsor must demonstrate with "substantial" evidence that the drug 1) "has a clinically meaningful effect and 2) exerts its effect on the 'core' manifestations of dementia." This requirement can be demonstrated by showing that the drug is superior when compared with a control in both 1) "a global assessment performed by a skilled clinician and 2) a performance based objective test instrument providing a

comprehensive assessment of cognitive functions." (Guidelines at 4.4.2) The requirement of improvement on a global assessment scale served, among other things, to "preclude the approval of drug products that produce no clinically meaningful effects on the overall status (e.g., health, function, etc) of demented patients, but do because of their pharmacologic activity, cause the detectable changes in patient performance on objective tests that are of uncertain clinical relevance." (Guidelines at 4.4.2.) The reported studies on physostigmine and tacrine did not, as of January 1986, show the sort of reliable, clinically meaningful improvements in Alzheimer's patients that would support the conclusion that a cholinesterase inhibitor would be therapeutically effective as a treatment for that disease.

B. Motivation to Combine

96. I do not believe a person of ordinary skill in the art would have been motivated at the time to combine the literature about physostigmine and tacrine in AD with the literature about galantamine use for other conditions so as to arrive at the conclusion that galantamine was a treatment for AD.

97. While the galantamine literature Drs. Domino and Levey cite describes galantamine as a possible treatment for a wide range of ailments, it is striking that none of the articles describes the drug as a treatment for dementia. In fact, the Pernov article describes its principal application as treatment for "diseases of the neuromuscular apparatus … and disease of the peripheral motoric neurons." (Mylan(GAL) 05984) This would teach away from its use for dementia, especially for a chronic, progressive condition such as AD, where central activity is required and peripheral effects would cast doubt on tolerability. Needless to say, AD is neither a disease of the neuromuscular apparatus nor one of the peripheral motoric neurons.

98. Drs. Levey and Domino appear to place great weight on galantamine's prior use to reverse the central effects of scopolamine. However, scopolamine induces a temporary

amnesia, not a chronic and progressive dementia. Utility for the former would not be viewed as very informative as to the latter, and indeed, there are scores of pharmacologic agents that address the central effects of scopolamine but are not treatments for AD.

99. R. Mohs et al. "Studies of Cholinergic Drug Effects on Cognition in Normal Subjects and Patients with Alzheimer's Disease," Aging 17:225-230 (1981), which Dr. Domino cites (Domino ¶ 42), criticizes reliance on a scopolamine model in Alzheimer's research. The authors note that the central effects of scopolamine involve a chemically-induced blockade of cholinergic receptors, which is quite different than AD: "we know of no disease in which memory is impaired due to cholinergic blockade. Alzheimer's disease appears to affect primarily the presynaptic functions of cholinergic neurons and affects receptors only to a lesser extent." (p. 229)

100. In short, the fact that galantamine, like physostigmine and other cholinergic agents, had efficacy in reversing the central effects of scopolamine would not suggest to one of ordinary skill in the art that galantamine was a substitute for physostigmine in treating Alzheimer's patents.

101. Drs. Levey and Domino suggest that the pharmacologic properties of galantamine made it an obvious substitute for physostigmine, most specifically with regard to galantamine's purported longer duration of action. In Dr. Domino's words, "one of skill in the art would have been motivated to combine the references based on the prior art teaching that galantamine was longer acting than physostigmine and there was a need for a longer-acting cholinesterase inhibitor as a clinical treatment for Alzheimer's disease." (Domino ¶ 91)

102. The position asserted by defendants' experts in this litigation is strikingly different than that taken by Dr. Domino in the published literature. In 1988, at a time when

galantamine was being studied as a treatment for AD, Dr. Domino reviewed the pharmacokinetic literature concerning galantamine and came to the very opposite conclusion from the one he asserts here:

> Especially clear, however, from their pharmacokinetic analysis is the fact that galanthamine is not a very long acting compound. This finding is consistent with our own unpublished studies on the comparative effects of physostigmine, tetrahydroaminoacridine, and galanthamine in suppressing self-stimulation behavior in the rat **where galanthamine is only as long acting as physostigmine but much less potent.** Domino, E.F., "Galanthamine: Another Look at an Old Cholinesterase Inhibitor," in Giacobini, E., and Becker, R., eds., Current Research in Alzheimer Therapy 295-303 (1988) (p. 301 (emphasis added)).

Clearly, a drug (like galantamine) that was seen as much less potent and no longer acting than physostigmine would not be viewed as a promising substitute for physostigmine in the treatment of AD, where the results from physostigmine itself were, at best, small and inconsistent.

103. As the foregoing suggests, a fair look at the chemistry and pharmacology of galantamine shows that one of ordinary skill in the art would not have been motivated to substitute it for physostigmine in the treatment of AD.

104. First, galantamine is chemically very different from physostigmine and tacrine, and has a different molecular structure. As Dr. Domino acknowledges, "each of these drugs differs structurally." (Domino ¶ 39) As one of ordinary skill would have recognized, these differences in structure can have profound effects on pharmacologic properties and activity and would render substitution of galantamine for physostigmine highly uncertain. Of course, as we now know, galantamine is quite different in its affects from physostigmine or tacrine. For example, galantamine has no meaningful inhibition on butyrylcholinesterase (a second cholinesterase enzyme found in the brain) and is only a weak inhibitor of acetylcholinesterase but has a substantial, positive allosteric modulatory effect on the nicotinic receptor.

105. In addition, a person of ordinary skill would not, in 1986, have viewed galantamine as a good substitute for physostigmine or tacrine in treating AD on the basis of its pharmacokinetics. Among other things, galantamine would be recognized as more than an order of magnitude less potent than physostigmine or tacrine. For example, a 1962 study by Boissier and Lesbros calculated that galantamine hydrobromide was 400-1000 times less active than neostigmine. Boissier, J. and Lesbros, J., "La galantamine, puissant cholinergique naturel. II-Activite anticholinesterasique de galanthamine et de quelques derives," Annales Pharmaceutiques Francaises. 2:150-155 (1962). (Translation, SYN RAZ 0022935-22943) Nesterenko (1965) observed that the acetylcholinesterase inhibitory effect of galantamine was 10-12 times less than that of physostigmine. L.N. Nesterenko, "Effect of Galantamine on the Acetylcholinesterase Activity of Various Regions of the Brain," Farmakologia I Toksikologia 28(4): 413-14 (1965) (Translation, SYN RAZ 13374-78) Tonkopii et al. (1976) compared the action of galantamine and tacrine on acetylcholinesterase from human erythrocyte and from brain slices of various animals. Their study showed that tacrine was about 100 times more potent against acetylcholinesterase than galantamine. Tonkopii, V.D. et al., "Interaction of reversible inhibitors with catalytic centers and allosteric sites of cholinesterases." Byulleten Éksperimental noi Biologii i Meditsiny, 82(8):947-950 (1976) (Translation, SYN RAZ-0013159-13162).

106. The literature available in 1986 reflects an understanding among researchers that galantamine is a weak cholinesterase inhibitor. As stated by Paskov (1986), "[t]he inhibitory effect of galanthamine on acetylcholinesterase . . . was found to be considerably lower than that of physostigmine and neostigmine." Paskov, D.S., "Galantamine," in D.A. Kharkevich ed., New Neuromuscular Blocking Agents, Vol. 79, Handbook of Experimental Pharmacology, 653-672

(1986), at 654. Mihailova (1985) also noted the weakness of galantamine's anticholinesterase effect. See D. Mihailova et al., "Modeling of Pharmacokinetic and Pharmacodynamic Behavior of Nivalin in Anaesthetized Cats," Methods and Findings in Experimental and Clinical Pharmacology 11:595-601 (1985).

107. This weaker cholinesterase inhibitory effect of galantamine would have discouraged drug developers from trying it as a treatment for AD. For example, the Mohs article, cited by Dr. Domino, also taught that high levels of cholinesterase inhibition were necessary to achieve positive results in Alzheimer's patients: "Improvement on memory tests while receiving physostigmine was highly correlated with the percent of inhibition in CSF: The patients who improved up to 40% on certain memory tests had a very high degree of cholinesterase inhibition, and patients with smaller improvements also had a smaller percent of cholinesterase inhibition." R.C. Mohs, et al., "Oral Physostigmine Treatment of Patients With Alzheimer's Disease," The American Journal of Psychiatry 142:28-33 (1985), at 32.

108. Moreover, concerns with galantamine's weak potency would not have been overcome by its duration of action. Although formal studies concerning galantamine's duration of action appear after Dr. Davis filed her patent application in January 1986, the literature pre-dating Dr. Davis' patent application indicates that the half-life of galantamine was not long. For example, in the literature cited by Drs. Domino and Levey, Bretagne, et al., "Essais Cliniques en Anesthésiologie D'un Nouvel Anticholinestérasique la Galanthamine," Anesthesie Analgesie Reanimation, 1: 285-92 (1971) notes that galantamine is "more transient in duration than that of neostigmine" (Translation, JAN RAZ 0134057) and that "the action of this product [galantamine] persists for over two hours." (Translation, JAN RAZ 0134061) This should be studied in contrast with reports of physostigmine's duration of action: Studies indicated that oral

physostigmine required dosing every 2 hours to achieve "steady state levels." R.C. Mohs et al., "Oral Physostigmine Treatment of Patients With Alzheimer's Disease," The American Journal of Psychiatry 142: 28-33 (1985) (p. 28). Also, it was observed that "the biologically effective half-life of orally administered physostigmine is undoubtedly much longer than previously suspected", L.J. Thal et al., "Oral Physostigmine and Lecithin Improve Memory in Alzheimer's Disease," Annals of Neurology 13:491-96 (1983) (p. 495).

109. A person of ordinary skill in January 1986 would not have viewed galantamine as clearly having a meaningfully longer duration of action than physostigmine for purposes of treating Alzheimer's disease, particularly in light of galantamine's substantially weaker potency. As Dr. Domino recognized in 1988, from the perspective of treating AD, galantamine is "only as long acting as physostigmine but much less potent." (Domino 1988, p. 301) Were a person of ordinary skill at the time interested in developing a drug with similar action as physostigmine but longer duration, the logical approach would be to develop a long-acting formulation of physostigmine itself, as Forest Laboratories attempted to do in developing Physostigmine SR®.

110. Finally, it is worth noting that none of the physostigmine or tacrine references cited by Dr. Levey or Dr. Domino suggest modifying their approach by using galantamine or another existing cholinesterase inhibitor. To the contrary, as reviewed above, the consistently expressed views in those papers were that physostigmine and tacrine were the best available cholinesterase inhibitors and that improvements beyond those compounds, if they were to be made, would come through development efforts to discover new cholinergic drugs or alternative therapeutic strategy. This too would discourage a person of ordinary skill from combining those references to use galantamine in lieu of physostigmine or tacrine.

C. Reasonable Expectation of Success

111. From the foregoing, it is also evident to me that a person of ordinary skill in the art in January 1986 would have not had a reasonable expectation of success in using galantamine to treat AD. As Dr. Levey euphemistically acknowledges, physostigmine itself was recognized to have "drawbacks." (Levey ¶ 36) Put more directly, and as discussed above, physostigmine was not viewed as a success, among other reasons because its effects were viewed as both inconsistent and, at best, marginal. In light of this, a person of ordinary skill would hardly have viewed galantamine as more promising, given that galantamine was, in Dr. Domino's words, "only as long acting as physostigmine but much less potent." (Domino 1988, p. 301).

112. In addition, as discussed in my opening report, there was considerable skepticism at the time of cholinesterase inhibitors as a treatment for AD. This skepticism, in fact, was well founded – as reviewed in that report, the vast majority of cholinesterase inhibitors (as well as essentially all other treatment approaches with the exception of memantine) failed. There is simply nothing in the galantamine literature cited by Drs. Levey or Domino that would have indicated to a person of ordinary skill that, unlike all these other attempts, galantamine would succeed.

VII. ENABLEMENT

113. Drs. Domino and Levey also assert that the '318 patent does not meet the "enablement" requirement of patent law because "it would not inform one of ordinary skill in the art that galantamine would be a therapeutically effective treatment for Alzheimer's disease." (Levey ¶ 120; See also Domino ¶¶ 26, 100-101) I disagree. First, the patent obviously states directly that galantamine is a therapeutically effective treatment for AD. Second, the patent provides the steps appropriate for confirming Dr. Bonnie Davis' insight concerning galantamine – most significantly, the manner of carrying out animal testing to confirm the proposed efficacy.

(See '318 patent, p. 2, col. 2, lns. 45-57) In addition, a person of skill in the art motivated by the patent to use galantamine as a treatment for AD would be enabled by the patent (and his or her own clinical knowledge) to use the drug for this purpose. For this reason, I believe that a person of ordinary skill would be able to carry out the claimed invention.

114. Drs. Levey and Domino also assert that claim 4 of the patent is not enabled because there is "no support for any dosage of galantamine at the high end of her range." (Levey ¶ 121; See Domino ¶¶ 26, 99) But a person of ordinary skill would have known, in reading her patent, how to adjust dosage so as to find a therapeutically effective dose of galantamine (or whichever salt of galantamine was being used) by following the standard practice of dose titration. The standard practice is to start the patient conservatively with a low dosage and then titrate to up to therapeutically effective dosage range. The patent itself recommends this practice. (See '318 patent, col. 1, lns. 64-66). Of course, we know from Razadyne® that there are doses of galantamine hydrobromide that are generally safe and effective within the range of claim 4 (albeit at the lower end of the range), and it seems clear to me that a person of ordinary skill would be able, using standard clinical practice, to titrate doses for his or her patients so as to find a therapeutically effective dose within the claimed range.

VIII. PROSECUTION OF THE '318 PATENT

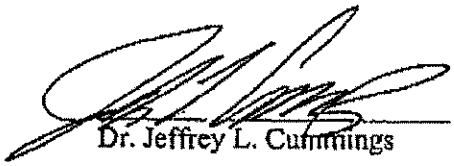
115. Finally, I note that both Dr. Levey and Dr. Domino criticize the way that the '318 patent was prosecuted in the Patent Office. I do not claim expertise in prosecuting patents, and I understand that the manner of patent prosecution is not relevant to the issues of anticipation, obviousness, and enablement. However, I have had the opportunity to review the patent prosecution and based on my expertise as a clinician and researcher in neurology, I disagree with Dr. Levey's and Dr. Domino's criticisms and find Dr. Davis' statements to the Patent Office to be a fair representation of the science.

116. For example, both Dr. Levey and Dr. Domino criticize Dr. Bonnie Davis for failing to cite the Bhasker article to the Patent Office. (Levey ¶ 125; Domino ¶ 63) I do not agree with their sentiments. As I discussed above, I believe the Bhasker article has no bearing on the treatment of Alzheimer's disease. In addition, I understand from Dr. Bonnie Davis' deposition that she was not even aware of the Bhasker article at the time she obtained the patent — a claim that I find entirely credible and reasonable as I had not heard of the Bhasker article until this litigation and as it is my understanding that the Bhasker article had never been indexed or cited at the time the patent was prosecuted.

117. Second, both Dr. Levey and Dr. Domino criticize Dr. Bonnie Davis's supposed failure to inform the Patent Office of the cholinergic hypothesis of Alzheimer's Disease and physostigmine studies conducted by Dr. Ken Davis and others . (Domino ¶ 59; see also Levey ¶ 126). That is incorrect. The cholinergic deficit associated with Alzheimer's disease is described in the patent in connection with its description of a good animal model for the disease, where the patent describes lesioned rats as having "a resultant cortical cholinergic deficiency, similar in magnitude to that seen in early to moderate stage Alzheimer's disease." ('318 patent, col. 2, lns. 45-50) In addition, it is my understand that Dr. Davis submitted a document to the Patent Office in connection with prosecuting the '318 patent in September 1986 entitled "Amendment Responsive to Office Action of April 10, 1986." In that document, Dr. Davis disclosed articles — Kendall, "Therapeutic Progress- Review XVIII Alzheimer's Disease," Journal of Clinical and Hospital Pharmacy, 10:327-36 (1985) and Hershenson and Moos, "Drug Development for Senile Cognitive Decline," Journal of Medicinal Chemistry, 29(7):1125-30 (1986). In addition, Dr. Davis noted in that document that physostigmine had "useful results."

(Amendment Responsive to Office Action of April 10, 1986 p.2). I believe that Dr. Davis' disclosure to the Patent Office was scientifically fair and reasonable.

Dated: Sept. 11, 2006



Dr. Jeffrey L. Cummings

ATTACHMENT A

Documents

1. United Kingdom Patent No. 942,200
2. United States Patent No. 4,663,318
3. Letter from Frantsits and Mucke to Bonnie Davis re: galanthamine patents [SYN RAZ 0000181]
4. Letter from Bonnie Davis to Alfred Gagne re: support for claim of galanthamine's superiority in treatment of Alzheimer's disease [SYN RAZ 0017587]
5. Letter from Bonnie Davis to Dr. William Cressman re: enclosed "new set of materials on the use of galanthamine for Alzheimer's disease" [SYN RAZ 0000761 -763]
6. Shire complaint filed in Vienna Commercial Court [SYN RAZ-0018366 - 18374]]
7. Amendment [of patent application] responsive to office action of April 10 [JAN RAZ-0000031-0000039]
8. Physician's Desk Reference (2006)
9. Deposition transcript of Dr. Bonnie Davis (February 8-9, 2006) and Exhibits

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EXHIBIT E

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

IN RE: '318 PATENT INFRINGEMENT LITIGATION	)	Civil Action No. 05-356-KAJ (Consolidated)

SECOND EXPERT REPORT OF DR. JOSEPH T. COYLE

I. INTRODUCTION

1. This report supplements my first expert report dated July 27, 2006. I was asked by Plaintiffs for this second report to review the opinions set forth in the reports by Drs. Edward Domino and Allan Levey dated July 27, 2006 and to provide my opinions concerning the validity of U.S. Patent No. 4,663,318 ("the '318 patent") in view of the defendants' claims that the patent is invalid due to anticipation, obviousness, or lack of enablement.

2. In addition to reviewing the reports submitted by Drs. Domino and Levey referenced above, I reviewed the documents discussed in those reports, and the materials referenced in my opening report and in Exhibit A to this report in forming my opinions as described herein. I also relied upon my experience in the field of neuropsychopharmacology and on my previous knowledge of the relevant scientific literature and state of the art.

II. LEGAL STANDARDS

3. To assist me in evaluating the defendants' expert reports and in forming my own opinions, counsel for plaintiffs have informed me of the legal standards governing the issues raised by the defendants' opening reports – anticipation, obviousness, and enablement.

A. Anticipation

4. I have been informed that the statutory requirement for anticipation of a patent claim is that the claimed invention must be shown to be "known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for patent." 35 U.S.C. § 102(a). Defendants' experts have asserted that the '318 patent was anticipated by an article published before Dr. Davis applied for her patent – P.A. Bhasker, "Medical Management of Dementia," The Antiseptic 71: 45-47 (1974) (the "Bhasker article"). In order for that article to anticipate claims 1 and 4 of the '318 patent, I understand that this article must describe the invention claimed in those patent claims. That is, the article must describe, to a person of ordinary skill in the art, each and every element of those claims.

5. Moreover, in order for the article to qualify as a "printed publication," I understand that the Bhasker article must be "publicly accessible." That is, it must be accessible to persons skilled or interested in the art. I understand that indexing of the article is relevant to determining whether it was accessible to persons skilled or interested in the art.

B. Obviousness

6. I have been informed that the following factors are relevant in determining whether a patent is invalid for reasons of obviousness: (1) the scope and content of the prior art; (2) the differences between the patented invention and the prior art; (3) the level of ordinary skill in the art; and (4) objective considerations of non-obviousness. I addressed objective considerations of non-obviousness in my opening report. In forming my opinion, I have also been asked to consider whether the prior art would have provided a person of ordinary skill a motivation to combine or modify the prior art references so as to arrive at the claimed invention

and also whether it would have provided such a person with a reasonable expectation of success in doing so.

C. Enablement

7. Finally, I understand that to be valid, a patent must enable a person skilled in the art to make and use the claimed invention. A patent is enabling if some experimentation is required, as long as the required experimentation is not unduly extensive.

III. LEVEL OF ORDINARY SKILL IN THE ART

8. In my opinion, in 1986, a person of ordinary skill in the art would have been a clinician with some experience in treating patients with Alzheimer's Disease – such a person would be the natural audience for a patent on a method of treating Alzheimer's disease. I believe that Drs. Domino and Levey overstate the level of skill that was "ordinary" at the time.

9. Historically, the fields of psychiatry and neurology have been quite distinct, and only in rare instances have clinicians or researchers been experienced or trained in both fields. As my co-authors and I described in B. Price et al., "Neurology and Psychiatry: Closing the Great Divide," Neurology 54: 8-14 (2000), researchers in neurology "laid claim to disorders of the nervous system with established etiologies and demonstrable anatomic pathology," while "[p]sychiatry pursued those disorders for which there was not visible pathology." (p. 8). In recent years, advances in the field of neuroscience – including advances relating to the study of Alzheimer's Disease – have provided compelling reason for collaboration if not integration of the two disciplines. However, as late as 2000, we were still calling for increased collaboration, and wrote that "given [] past problems" caused by the gulf between the two fields "it is now not only possible but necessary to emphasize the integration of neurology and psychiatry." (p. 10).

10. Therefore, it is my opinion that a person of "ordinary" skill in the art in 1986 would not have had training or experience in both fields. Instead, I believe that such a person of

"ordinary" skill for purposes of the '318 patent would have been a clinician with some experience treating Alzheimer's patients, but limited knowledge or experience of neurochemistry (or neuropharmacology). For purposes of this report, however, I accept Drs. Domino's and Levey's characterizations of the person of ordinary skill in the art because doing so does not alter my opinion that the '318 patent is not invalid for reasons of anticipation, obviousness, or lack of enablement.

IV. ANTICIPATION

11. Drs. Levey and Domino both assert that an article by P.A. Bhasker, "Medical Management of Dementia," The Antiseptic, 71: 45-47 (1974) (the "Bhasker article") anticipates Claims 1 and 4 of the '318 patent. (Levey ¶¶ 20, 70-72, 99-102; Domino ¶¶ 22, 63, 79-80). I respectfully disagree with this conclusion, and I disagree with their interpretation of the article. In my opinion, a person of ordinary skill – whether reading the article now or in 1986 – would not understand the article to suggest the use of galantamine for the treatment of Alzheimer's Disease. If anything, given its statement that progressive dementias are not treatable, a person reading the article would have been discouraged from trying galantamine for the treatment of the disease.

A. Summary of the Bhasker article

12. In summary, the Bhasker article describes treatment for certain forms of dementia. However, it distinguishes treatable forms of dementia from those forms of dementia that Bhasker considers to be untreatable, and it emphasizes the importance of distinguishing these forms in patients. With respect to dementias more generally, the article considers treatment prognosis to be "gloomy" except in cases where "one of the treatable underlying causes is detected." (p. 45). Treatable or "reversible" causes, according to Bhasker, include "cases of

tumours (when removable), infections (like GPI) when they can be "successfully" arrested, post-traumatic dementias, and low pressure hydrocephalus." (p. 45).

13. In contrast to such treatable forms of dementia, "[t]he irreversible cases belong to the category of dementias where there is a progressive fall-out of neurons and the course of the illness is rapidly downhill." (p. 45). Bhasker makes clear that he considers progressive dementias to fall in the category of untreatable dementias. He writes: "**With regard to progressive dementia**, there appears very little to offer. Only management and **no treatment is (sic) possible**." (Id.).

14. The article emphasizes the importance of determining into which of these two categories a patient's dementia falls. "[T]he importance of a thorough diagnosis even at the first instance must be realised, because the compartmentalisation into treatable and untreatable dementias has to be made with the utmost care." (p. 45).

15. The Bhasker article's only reference to galantamine is in connection with reporting Luria's work in treating "local brain damage." Specifically, the article states that:

> The restoration of higher cortical functions is difficult and was once considered to impossible; but it has lately gained importance. Luria and his colleagues have dealt with this problem *in great detail. They have suggested measures of improving the* higher functions in cases of local brain damage like tumour, head injury, infarct etc, by deinhibitory procedures and re-education of the rest of the brain. Deinhibition refers to the facilitation of acetylcholine activity by giving small daily doses of Cholinesterase inhibitors (Neostigmine, Gallanthamine etc.). (p. 46).

16. By referring to "Luria and his colleagues," I understand Bhasker to be referring to the Soviet neurologist, Dr. Alexander Luria, although the precise work or reference to which Bhasker refers is not stated. Dr. Luria's work principally related to the study of aphasia and other disorders in individuals suffering from local brain injury, as exemplefied by the Luria publication cited by Dr. Levey (Luria et al., "Restoration of Higher Cortical Function Following

Local Brain Damage," in P.J. Vincken and G.W. Bruyn, eds., Handbook of Clinical Neurology, vol. 3, pp. 368-433 (1969), (Levey ¶¶ 72-73)).

17. The Luria publication cited by Dr. Levey does not discuss Alzheimer's Disease, and the passage of the article that Dr. Levey's report quotes is inapplicable to the disease. Dr. Levey quotes the article as stating: "**pharmacological 'deblocking' therapy can reactivate temporarily inhibited cells** and thereby contribute to the successful restoration of brain functions." (Levey ¶ 72 (emphasis added)). However, Alzheimer's Disease and related dementias do not involve such "temporarily inhibited cells" – rather, they involve cell death and *irreversible loss of neurological function.*

18. I am not aware of Dr. Luria having ever studied the treatment of Alzheimer's Disease or his work being cited in that context.

B. Bhasker as it relates to anticipation

19. In my opinion as a neuropsychopharmacologist, a person of ordinary skill in the art would not understand the Bhasker article to propose galantamine for the treatment of Alzheimer's Disease, whether reading the article in 1986 or today. As I will discuss, a person of ordinary skill in the art would understand the article to be saying that "progressive" dementias are untreatable. Because Alzheimer's Disease is a progressive dementia, the Bhasker article – to the extent it suggests anything at all about Alzheimer's Disease – suggests that no treatment for the condition is available. I therefore disagree with the assertions of Drs. Levey and Domino that the Bhasker article anticipates the claims of the '318 patent.

20. As an initial matter, the article never mentions Alzheimer's Disease by name. While the article does reference "irreversible" or "progressive" dementia – a reference Drs. Domino and Levey interpret as encompassing Alzheimer's disease (Levey ¶ 99; Domino ¶ 79) – the description of such dementia expressly set forth in the Bhasker article excludes Alzheimer's

Disease. Bhasker refers to progressive dementias with a "rapidly downhill" course. (p. 45). This would not include Alzheimer's, the progression of which is typically rather slow. From the perspective both of clinical diagnosis and pharmacological treatment, progressive dementias with a rapid course are quite different from those with a slow progression. A person of ordinary skill, whether a clinician or a pharmacologist, would not have understood Bhasker's description of dementias with a rapid downhill course to relate to Alzheimer's Disease.

21. In addition, the Bhasker article's sole reference to galantamine does not even relate to progressive dementias. To the contrary, the article's single reference to galantamine is made in its discussion of "deinhibitory" treatment measures for "local brain damage." Specifically, the Bhasker article states that Luria and his colleagues "**have suggested measures of improving the higher functions in cases of local brain damage like tumour, head injury, infarct etc, by deinhibitory procedures and re-education of the rest of the brain.** Deinhibition refers to the facilitation of acetylcholine activity by small daily doses of cholinesterase inhibitors (Neostigmine, Gallanthamine etc.)." (Bhasker, at p. 46 (emphasis added)).

22. From a neuropsychopharmacological standpoint, "local brain damage" such as "tumour, head injury, infarct etc." is entirely different from the condition of the brain diagnosed as Alzheimer's Disease. "Local brain damage" caused by "tumour, head injury, [or] infarct" would be characterized by acute, localized injury to brain cells, whereas Alzheimer's Disease results in slow, chronic decline ultimately resulting in cell death. From a neuropharmacologic standpoint, treatment of local brain damage is very different from treatment of Alzheimer's disease, and a person of ordinary skill reading Bhasker's suggestion of galantamine for local

brain damage would not have understood that suggestion to be applicable to Alzheimer's Disease.

C. Inaccessibility of the Bhasker article

23. In addition, the Bhasker article was not accessible to persons of ordinary skill in the art in 1986. The Indian journal in which it appeared, The Antiseptic, is not a reference that clinicians or researchers would have reviewed in the ordinary course of their work.

24. Moreover, a researcher working in the field of neuropharmacology in 1986 would not have found the Bhasker article through the normal channels of scientific research. Such a researcher would have used a medical index and would have reviewed the relevant, standard scientific journals.

25. Neither of these channels would have brought the Bhasker article to the attention of a researcher in neuropharmacology, much less a clinician treating some patients with Alzheimer's Disease. In 1986, the standard was the Index Medicus, a monthly guide to articles published in approximately 4,000 journals. The Antiseptic was not included in the Index Medicus. Nor was the Bhasker article cited by any scientific literature available at the time. In my opinion, even a diligent researcher in 1986 would not have found the article.

26. Over the course of my career, I have read scores of articles in the fields of neurology, pharmacology, and Alzheimer's Disease. Before I was shown the article in connection with this litigation, I had never seen or heard of the Bhasker article, nor had I heard of the journal in which it appeared, the Antiseptic, a medical journal published in India. In my opinion, that article was not publicly accessible.

V. NON-OBVIOUSNESS

A. Differences between the prior art and the patented invention

27. I understand that for purposes of assessing whether a patented invention is obvious, the relevant analysis is a comparison of disclosures contained in the prior art to the claims of the patented invention, which are described in my opening report. (See Coyle ¶ 18-20).

28. I have reviewed the prior art cited by Drs. Domino and Levey, as well as additional references (which are listed in Exhibit A). Based on that review, as well as my experience and knowledge in the field of pharmacology, it is my opinion that the prior art did not render the '318 patent obvious. The patent is not obvious for two primary reasons. First, the prior art did not suggest that any drug was therapeutically effective in treating Alzheimer's Disease. Second, the prior art also did not suggest galantamine or its salts as a treatment for Alzheimer's Disease, let alone describe it as a therapeutically effective treatment.

29. I understand the reports of Drs. Domino and Levey to assert that physostigmine and tacrine had been shown by 1986 to be therapeutically effective treatments for Alzheimer's Disease. However, it is clear from a review of the relevant neuropharmacological literature that proper agents for treating Alzheimer's Disease had not been identified at that time.

30. Drs. Domino and Levey base their assertions on certain published studies of the drugs, such as those reported in the articles of Dr. Mohs. (Levey ¶ 116, Domino ¶ 42). However, the work of Dr. Mohs expressed pessimism concerning the therapeutic effectiveness of cholinesterase inhibitors and of cholinergic drugs more generally.

31. For instance, in the 1981 publication R. Mohs, et al., "Studies of Cholinergic Drug Effects on Cognition in Normal Subjects and Patients with Alzheimer's Disease," Aging 17: 225-30 (1981), the authors reviewed various pharmacologic attempts to enhance cholinergic

function as a means to treat Alzheimer's Disease and concluded "[a]t present it is not clear whether studies of cholinergic drugs will lead to useful treatments for any of the debilitating dementias that afflict so many people." (p. 229).

32. Four years later, in November 1985, in R.C. Mohs, et al., "Clinical Studies of the Cholinergic Deficit in Alzheimer's Disease," J. Amer. Geriatrics. Soc. 33: 749-57 (1985), the authors again expressed skepticism that a cholinergic approach such as a cholinesterase inhibitor would prove clinically beneficial:

> Combining careful biologic assessment and clinical diagnosis with attention to the unique pharmacologic properties of cholinergic drugs may ultimately identify a group of AD/SDAT patients who can derive meaningful clinical benefit from cholinesterase inhibitors or choliergic agonists. However, it must be recognized that even when these conditions are met, the use of such drugs could be severely limited. It has been pointed out, for example, that cholinergic cells have relatively few postsynaptic projections that are nonoverlapping, so that it is difficult for surviving cholinergic cells to compensate functionally for lost cells by increasing their firing rate. In addition, none of these drugs may be able to duplicate the phasic action of cholinergic cells in transmitting information. If such considerations prove to be true then any pharmacotherapy of AD/SDAT may have to depend on manipulation of transmitters and cotransmitters operating at sites postsynaptic to the dying neurons. Whatever these pharmacologic methods may be, considerations such as those described in this paper will be important in the design and interpretation of clinical studies. (p. 756).

33. My own work from around that time similarly demonstrates that from a pharmacological standpoint, neither the proper pharmacologic approach nor the proper agent had been found. In J.T. Coyle, et al., "Alzheimer's Disease: A Disorder of Cortical Cholinergic Innervation," Science 219: 1184-1190 (1983), my co-authors and I reviewed the state of research concerning Alzheimer's Disease as it existed at the time, particularly in view of the cholinergic deficit hypothesis. We observed that the brains of patients with Alzheimer's Disease showed a loss of nerve cells, and that neurochemical studies indicated that presynaptic cholinergic markers and activity of the acetylcholinesterase enzyme are reduced in the cerebral cortex and hippocampus of affected individuals.

34. Our article also compared Alzheimer's Disease to Parkinson's Disease, which is characterized by a deficiency in dopamine and may be treated with the dopamine precursor, L-dopa. Using this analogy, we suggested that pharmacologic strategies for treating Alzheimer's Disease could include administration of acetylcholine precursors, cholinesterase inhibitors, or post-synaptic muscarinic receptor agonists. (p. 1188). Reviewing the literature, however, we concluded that, in contrast to the results in treating Parkinson's Disease, "[t]hus far, **the results [in treating Alzheimer's] have been rather inconclusive** although a few reports indicate that some patients, primarily in the early stages of AD, may experience modest improvements in cognitive functions." (p. 1189) (emphasis added). We attributed this relative lack of response to "important differences in the synaptic organization and physiology of the two affected neuronal systems." (p. 1189).

35. Another article cited in Dr. Levey's report (Levey ¶ 32) expressed a similar view concerning the analogy of potential treatments for Alzheimer's Disease to treatments for Parkinson's Disease. B.S. Greenwald, et al., "Neurotransmitter Deficits in Alzheimer's Disease: Criteria for Significance," J. Amer. Geriatrics Soc., 31(5): 310-16 (1983), reviewed the work on cholinesterase inhibitors and other cholinergic enhancement approaches and acknowledged that these approaches had not resulted in a therapeutically effective treatment for Alzheimer's Disease. They agreed that although "L-dopa and other agonists can ameliorate symptoms in [Parkinson's Disease] patients, the effects of cholinergic-enhancing compounds in AD are much more limited. Encouragingly, positive effects of cholinomimetics have been reported; however, a level of clinical utility has not been achieved." (p. 313). They posited as "[p]ossible explanations for this differential effect by [dopamine] and [acetylcholine] agonists in [Parkinson's Disease] and AD, respectively": that "(a) cholinergic neurons are regulated

differently than are dopaminergic neurons, (b) neurochemical deficits are more complex in AD than in PD, and (c) currently available cholinergic agents are unable to substantially influence symptoms of AD." (p. 313).

36. Still other articles among those cited by Drs. Domino and Levey discussed the pharmacological limitations of cholinergic agents, including the limitations of cholinesterase inhibitors in particular, that rendered therapeutic effectiveness for Alzheimer's Disease unlikely. C. Johns, et al., "The Cholinergic Treatment Strategy in Aging and Senile Dementia," Psychopharmacology Bulletin, 19(2): 185-97 (1983), cited by Dr. Domino at ¶¶ 35, 85, reviewed the role of the cholinergic hypothesis in treatment strategies for Alzheimer's Disease, including possible uses of acetylcholine precursor therapy in connection with metabolic enhancers such as piracetam, guanidine, or 4-amino-pyridine (p. 188), the cholinesterase inhibitors physostigmine and THA (pp. 189-92), and the muscarinic receptor agonists arecoline and oxotremorine. (p. 187).

37. With regard to the cholinesterase inhibitors, the authors reviewed the inconsistent results achieved with cholinesterase inhibitors at the time and suggested that agonists might be more promising than cholinesterase inhibitors because, unlike precursor therapy or cholinesterase inhibitors, post-synaptic receptor agonists do not depend upon the (impaired) presynaptic cholinergic system for their effects:

> Both strategies [precursors and inhibitors], however, share a fundamental limitation in that they are dependent on an intact presynaptic neuron to provide a substrate for their activity. These problems may be circumvented by administering cholinergic agents which work directly at postsynaptic receptor sites, since the number of postsynaptic muscarinic binding sites is not reduced in SDAT patients as compared to age-matched controls. (p. 192).

38. Overall, they concluded that "[t]he success of cholinomimetic treatment strategies thus far has been modest, and definitive treatment of SDAT awaits clarification of complex

neurochemical variables, delineation of parameters that can predict response, and development of appropriate safe, long-acting pharmacologic agents." (p. 193).

39. In short, none of the articles cited by Drs. Levey and Domino show that physostigmine or any other drug or drug class was therapeutically effective for the treatment of Alzheimer's Disease. Put in the context of the prevailing skepticism of cholinesterase inhibitors at the time and the preference for other approaches, as I reviewed in my opening report, I do not believe a person of ordinary skill would have viewed the prior art as describing a cholinesterase inhibitor approach as therapeutically effective for treating Alzheimer's Disease.

B. Motivation to Combine

40. In my opinion, a person of ordinary skill in the art in 1986 would have lacked a motivation to combine the prior art in such a way as to conclude that galantamine would be a therapeutically effective treatment for Alzheimer's Disease. That is, contrary to the assertions by Drs. Domino and Levey, the literature concerning the use of physostigmine and tacrine for Alzheimer's Disease and the literature concerning the use of galantamine for unrelated purposes did not render use of galantamine for the treatment of Alzheimer's Disease obvious. In particular, the pharmacological properties of galantamine would not have made it an appropriate or obvious substitute for physostigmine or tacrine as a treatment for Alzheimer's.

41. The literature that describes galantamine as active in the peripheral and neuromuscular systems in fact points away from galantamine as a treatment for Alzheimer's Disease. The Pernov article cited by both Drs. Domino and Levey (Domino ¶¶ 37, 87; Levey ¶¶ 81, 83, 103, 115-116) is a good example of this. See K.G. Pernov, "Nivalin and its Curative Effect Upon Diseases of the Nervous System," Psychiatry, Neurology and Medical Psychology Bulletin on Research and Practice, 13(11): 416-20 (1961). Pernov describes galantamine as "above all" a treatment for "diseases of the neuromuscular apparatus … and disease of the

peripheral motoric neuron." (Mylan(GAL) 05984). This would not logically lead to a recommendation of galantamine's use for dementia, and in particular for Alzheimer's Disease, since activity in the central nervous system is required for treating Alzheimer's Disease and activity in peripheral systems would suggest unwanted side effects and poor tolerability of the drug.

42. The literature on scopolamine, heavily emphasized in the reports of Drs. Domino and Levey, does not support galantamine for use in treating Alzheimer's Disease. Although scopolamine is an agent that acts on a sub-population of acetylcholine receptors in the central nervous system, it induces a condition that bears little resemblance to Alzheimer's Disease. Scopolamine induces a temporary delirium or amnesia in patients, not a chronic and progressive dementia.

43. The prior art, including one of the articles cited by Dr. Domino, R. Mohs et al. "Studies of Cholinergic Drug Effects on Cognition in Normal Subjects and Patients with Alzheimer's Disease," Aging 17: 225-30 (1981) (Domino ¶ 42), reflects criticism of using a scopolamine model for conducting research into the treatment of Alzheimer's Disease. Mohs et al. express skepticism of relying upon a scopolamine model for drug development because of the differences between the two conditions. Introduction of scopolamine results in a chemically-induced blockade of cholinergic receptors. However, there is "no disease in which memory is impaired due to cholinergic blockade" as with scopolamine. (p. 229). Alzheimer's Disease, by contrast, "appears to affect primarily the presynaptic functions of cholinergic neurons and affects receptors only to a lesser extent." (Id.).

44. In light of the differences between scopolamine-induced conditions and the chronic, progressive condition of Alzheimer's Disease, the fact that galantamine was efficacious

in reversing the temporary effects of scopolamine would not have suggested to a person of ordinary skill in the art that galantamine would be a therapeutically effective substitute for physostigmine in the treatment of Alzheimer's Disease.

45. The conclusions drawn by Drs. Domino and Levey rest heavily on the proposition that a single pharmacological attribute of galantamine – its duration of action – made it an obvious substitute for physostigmine as a treatment for Alzheimer's Disease. Dr. Domino, for example, writes that "one of skill in the art would have been motivated to combine the references based on the prior art teaching that galantamine was longer acting than physostigmine and there was a need for a longer-acting cholinesterase inhibitor as a clinical treatment for Alzheimer's disease." (Domino ¶ 91).

46. However, this oversimplifies the analysis of galantamine from a pharmacological perspective. In my opinion, the pharmacologic, including pharmacokinetic, properties of galantamine did not make it an obvious substitute for physostigmine as a treatment for Alzheimer's Disease. The literature and what was known about the pharmacological profile of galantamine at the time did not suggest that galantamine was a suitable substitute for physostigmine, or even that it was an ideal candidate for further testing.

47. First, galantamine is chemically very different from physostigmine and tacrine, and has a different molecular structure. As Dr. Domino acknowledges, "each of these drugs differs structurally." (Domino ¶ 39). As one of ordinary skill would have recognized, these differences in molecular structure can have profound effects on pharmacologic properties and activity and would render substitution of galantamine for physostigmine highly uncertain. Of course, as we now know, galantamine is quite different in its affects from physostigmine or tacrine. For example, galantamine has no meaningful inhibition on butyrylcholinesterase (a

second cholinesterase enzyme found in the brain) and is only a weak inhibitor of acetylcholinesterase but has a substantial, positive allosteric modulatory effect on the nicotinic receptor.

48. Second, galantamine would not have been known by a person of ordinary skill in 1986 to have a clinically optimal half-life for purposes of treating a steadily progressive dementia such as Alzheimer's Disease. In 1986, a researcher in pharmacology, much less a clinician treating some patients with Alzheimer's Disease, was not likely to be aware of galantamine's duration of action, because the pharmacokinetics of the substance had not yet been systematically measured. The literature and measurements available at the time would not have suggested to one of ordinary skill in the art that galantamine was a particularly long-acting substance. For example, Bretagne et al., in their article describing their study of the decurarizing effect of galantamine in 50 post-surgical patients, noted that "the action of this product [galantamine] persists for over two hours" and that none of the patients in their study underwent a recurarization. Bretagne, et al., "Essais Cliniques en Anesthesiologie d'un Nouvel Anticholinesterasique la Galanthamine," Anesthesie Analgesie Reanimation, 1: 285-92 (1971) (Translation at JAN RAZ 0134061).

49. At the same time, the literature available in 1986 did not suggest that the duration of action of physostigmine was meaningfully shorter. Mohs et al. (1985), for example, recommended dosing of physostigmine every two hours. R.C. Mohs et al., "Oral Physostigmine Treatment of Patients With Alzheimer's Disease," Am. J. Psychiat. 142: 28-33 (1985). Thal et al. (1983) simply noted that "the biologically effective half-life of orally administered physostigmine is undoubtedly much longer than previously suspected." L.J. Thal et al., "Oral

Physostigmine and Lecithin Improve Memory in Alzheimer's Disease," Ann. Neurol. 13: 491-96 (1983), at 495.

50. In view of this literature, a person of ordinary skill in the art would not have viewed galantamine as meaningfully longer acting than physostigmine from the standpoint of clinical utility in treating Alzheimer's Disease. An article authored by Dr. Domino himself in 1988 expressly reflects the thinking that galantamine was not longer acting than physostigmine for that purpose. E.F. Domino, "Galanthamine: Another Look at an Old Cholinesterase Inhibitor," in Giacobini, E., and Becker, R., eds., Current Research in Alzheimer Therapy, pp. 295-303 (1988). In this article, Dr. Domino reviewed the pharmacokinetics of galantamine in connection with possible evaluation of its use in treating Alzheimer's Disease (that was after, for example, the animal studies conducted in my laboratory were published). He concluded that galantamine was "not a very long acting compound" and in fact was "only as long acting as physostigmine but much less potent." (p. 301).

51. It is telling that the articles cited by Drs. Domino and Levey as describing galantamine as a longer-acting substitute for physostigmine do so in the context of conditions, such as scopolamine-induced amnesia, which are temporary in nature and involve acute rather than chronic administration of therapy. The pharmacologic considerations for such treatments are very different than those for treatment of Alzheimer's Disease. Hence, suggestions that galantamine was a longer-acting or appropriate substitute for physostigmine in the context of such temporary or acute conditions would not lead one of ordinary skill to conclude the galantamine was also a sufficiently long acting or appropriate substitute for physostigmine in the very different context of Alzheimer's Disease – as Dr. Domino's 1988 publication expressly confirms.

52. Third, as Dr. Domino's article also shows, galantamine was well-known in the literature at the time to be a relatively weak cholinesterase inhibitor – as more than an order of magnitude less potent than physostigmine, tacrine, or other cholinesterase inhibitors. Nesterenko (1965) observed that the acetylcholinesterase inhibitory effect of galantamine was 10-12 times less than that of physostigmine. L.N. Nesterenko, "Effect of Galanthamine on the Acetylcholinesterase Activity of Various Regions of the Brain," Farmakologia I Toksikologia 28(4): 413-14 (1965) (Translation at SYN RAZ 0013374). And Tonkopii et al. (1976) compared the action of galantamine and tacrine on acetylcholinesterase from human erythrocyte and from brain slices of various animals. Their study showed that tacrine was about 100 times more potent against acetylcholinesterase than galantamine. V.D. Tonkopii, et al., "Interaction of Reversible Inhibitors with Catalytic Centers and Allosteric Sites of Cholinesterases." Bull. Exp. Biol. Med. 86: 400-01 (1976). Finally, a 1962 study by Boissier and Lesbros calculated that galantamine hydrobromide was 400-1000 times less active than neostigmine. J. Boissier & J. Lesbros, "La galantamine, puissant cholinergique naturel. II-Activité anticholinesterasique de galanthamine et de quelques derivés," Ann. Pharm. Fr. 2: 150-55 (1962).

53. The literature available in 1986 reflects an understanding of galantamine as a weak cholinesterase inhibitor. As stated by Paskov (1986), "[t]he inhibitory effect of galanthamine on acetylcholinesterase . . . was found to be considerably lower than that of physostigmine." D.S. Paskov, "Galantamine," in D.A. Kharkevich (ed.), New Neuromuscular Blocking Agents, Vol. 79, Handbook of Experimental Pharmacology, pp. 653-672 (1986), at p. 654. Mihailova et al. (1985) also noted the weakness of galantamine's anticholinesterase effect. D. Mihailova et al., "Modeling of Pharmacokinetic and Pharmacodynamic Behavior of Nivalin in Anaesthetized Cats," Methods Find. Exptl. Clin. Pharmacol. 11: 595-601 (1985).

54. This weaker cholinesterase inhibitory effect of galantamine would have discouraged drug developers from trying it as a treatment for Alzheimer's Disease, because the literature at the time reflected a concern in the field for achieving sufficiently high cholinesterase inhibitory effect. For example, the Mohs article, cited by Dr. Domino, stated that high levels of cholinesterase inhibition were necessary to achieve positive results in Alzheimer's patients: "Improvement on memory tests while receiving physostigmine was highly correlated with the percent of inhibition in CSF: The patients who improved up to 40% on certain memory tests had a very high degree of cholinesterase inhibition, and patients with smaller improvements also had a smaller percent of cholinesterase inhibition." R.C. Mohs, et al., "Oral Physostigmine Treatment of Patients With Alzheimer's Disease," Am. J. Psychiat. 142: 28-33 (1985), at p. 32.

55. Clearly, a drug (like galantamine) that was seen at the time as much less potent than physostigmine, and not clearly longer acting, would not be viewed as a promising substitute for physostigmine in the treatment of Alzheimer's Disease, especially where the results from physostigmine itself were, at best, small and inconsistent. Instead, were a person of ordinary skill at the time interested in developing a drug with similar effects as physostigmine but a longer duration of action – as Drs. Domino and Levey assert – the logical course for such a person would have been to develop a longer acting formulation of physostigmine (as Forest Laboratories ultimately did, albeit unsuccessfully).

56. Finally, it is worth noting that none of the physostigmine or tacrine references cited by Dr. Levey or Dr. Domino suggest modifying their approach by using galantamine or another existing cholinesterase inhibitor. To the contrary, as even the articles cited by Drs. Levey and Domino confirm, the consistently expressed views in those papers were that physostigmine and tacrine were the best available cholinesterase inhibitors and that

improvements beyond those compounds, if they were to be made, would come through efforts to develop new cholinergic drugs altogether. For example, R. Mohs, et al., "Studies of Cholinergic Drug Effects on Cognition in Normal Subjects and Patients with Alzheimer's Disease," Aging 17: 225-30 (1981), states expressly that "no safe long-acting cholinesterase inhibitor is available at the present time." (p. 226-227). B.S. Greenwald, et al., "Neurotransmitter Deficits in Alzheimer's Disease: Criteria for Significance," J. Amer. Geriatrics Soc., 31(5): 310-16 (1983), warns that "currently available cholinergic agents are unable to substantially influence symptoms of AD." (p. 313). This too would have discouraged a person of ordinary skill from modifying those references to use galantamine in lieu of physostigmine or tacrine.

C. Reasonable Expectation of Success

57. From the foregoing, it is also evident to me that a person of ordinary skill in the art in January 1986 would have not had a reasonable expectation of success in using galantamine to treat Alzheimer's Disease. In particular, the results of the physostigmine trials did not establish proof of concept that cholinesterase inhibitors would work in treating Alzheimer's Disease; the outcomes of those trials were equivocal and inconsistent. In view of these results, a person of ordinary skill, if anything, would have perceived galantamine to be less likely of achieving success than physostigmine, because it is "only as long acting as physostigmine but much less potent." (Domino (1988), at p. 301).

58. My opinion that a person of ordinary skill would not have had a reasonable expectation of success in the patented invention is further supported by the skepticism of a cholinesterase inhibitor approach (and other cholinergic approaches) to treating Alzheimer's Disease that was prevalent in the field at the time. Such skepticism was described in my opening report. (Coyle ¶¶ 41-49).

VI. ENABLEMENT

59. Dr. Levey also asserts that the '318 patent does not meet the "enablement" requirement of patent law because the patent does not provide sufficient evidence to show that galantamine would be a therapeutically effective treatment for Alzheimer's Disease. (Levey ¶ 120). In my view, this assertion is incorrect; rather, the claims of Dr. Bonnie Davis's patent disclose sufficient information to permit one of skill in the art to make or use her invention.

60. In particular, the patent describes the next steps that a researcher should take in order to confirm and put into practice Dr. Davis's invention concerning galantamine. That is, she describes the animal testing needed to confirm the efficacy of the drug:

> The following test provides a good animal model for Alzheimer's disease in humans: A selective lesion is placed in a subcortical nucleus (nucleus basalis of Meynert) with a resultant cortical cholinergic deficiency, similar in magnitude to that seen in early to moderate stage Alzheimer's disease. . . . Drugs that can normalize these abnormalities would have a reasonable expectation of efficacy in Alzheimers' disease. ('318 patent, p. 2, column 2, ll. 45-54).

61. In fact, my laboratory performed the animal studies described by Dr. Davis. We studied the impact of galantamine on the working memory of mice with lesions in the nucleus basalis of Meynert. J. Sweeney, et al., "A Long-Acting Cholinesterase Inhibitor Reverses Spatial Memory Deficits in Mice," Pharmacology Biochemistry & Behavior 31: 141-47 (1988). As a result of the studies, we concluded that "[g]alanthamine [] can significantly improve performance of a spatial memory task in nBM-lesioned animals" and that "appropriate pharmacological manipulations of the cholinergic system" could be "developed to alleviate some of the cognitive impairments associated with dementia, such as that seen in Alzheimer's Disease." (p. 146). In subsequent studies of the impact of different doses of galantamine on the working memory of the lesioned mice, we again concluded that "galanthamine may have therapeutic utility in attenuating the cholinergic deficits in the early stages of Alzheimer's

Disease." J. Sweeney et al., "Effects of Different Doses of Galanthamine, a Long-Acting Acetylcholinesterase Inhibitor on Memory in Mice," Psychopharmacology 102: 191-200 (1990), at p. 199.

62. Besides helping to confirm the efficacy of Dr. Davis's invention, the results of our animal studies were used in regulatory submissions that ultimately resulted in the approval of galantamine for the treatment of Alzheimer's and opened the door for development, marketing, and patient use of Razadyne®.

63. Both Drs. Domino and Levey also assert that claim 4 of the patent is not enabled because there is "no support for any dosage of galantamine at the high end of her range." (Levey ¶ 121; see also Domino ¶ 97). However, a person of ordinary skill in the art reading the '318 patent would have known how to adjust the dosage so as to arrive at a therapeutically effective dose of galantamine (or one of its salts) – that is, such a person of ordinary skill would have titrated the dose, which is exactly what the patent instructs. (See '318 patent, col. 1, lns. 64-66). The standard clinical practice of dose titration is to start the patient conservatively with a low dosage and then to slowly increase the dosage to arrive at a therapeutically effective dosage range. In my opinion, the patent provides sufficient information to enable a person of ordinary skill to use this standard procedure and arrive at an appropriate dose range for galantamine.

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64. Finally, I write to address briefly Drs. Domino's and Levey's criticism of Dr. Davis's prosecution of patent application, even though I do not understand it to be relevant to any issues in the case.

65. In my opinion, Dr. Davis's statements made to the Patent Office were scientifically fair and reasonable. First, the fact that Dr. Davis did not cite the Bhasker article to

the Patent Office is both reasonable and unsurprising. As I have discussed above, that article has nothing to do with Alzheimer's Disease. Also, I understand that she was not aware of the article at the time she submitted her patent application, which reflects the obscurity of the article and not a lack of diligence on her part.

66. Second, Drs. Domino and Levey are incorrect that Dr. Davis failed to bring to the Patent Office's attention the cholinergic hypothesis. The cholinergic deficiency in Alzheimer's is discussed expressly in the '318 patent. Specifically, in column 2, she describes as "a good animal model for Alzheimer's disease in humans" the use of nbM-lesioned rats, which lesions cause "a resultant cortical cholinergic deficiency, similar in magnitude to that seen in early to moderate stage Alzheimer's disease." ('318 patent, col. 2, lns. 48-50). This states directly, of course, that Alzheimer's Disease is characterized by a "cortical cholinergic deficiency," and that is also the clear logic of the animal model she proposes.

67. In addition, in her "Amendment Responsive to Office Action of April 10, 1986," which I understand she submitted to the Patent Office in September 1986, she cited and attached two review articles about Alzheimer's Disease that address the cholinergic hypothesis and discuss the studies on cholinesterase inhibitors – Kendall, "Therapeutic Progress- Review XVIII Alzheimer's Disease," Journal of Clinical and Hospital Pharmacy, 10:327-36 (1985) and Hershenson and Moos, "Drug Development for Senile Cognitive Decline," Journal of Medicinal Chemistry, 29(7): 1125-30 (1986).

68. Finally, I disagree with Dr. Domino that the "proper analogy" for cholinesterase inhibitor therapy is the treatment of diabetes with insulin. (Domino ¶ 58). Insulin therapy in diabetes involves supplementation of the insulin-deficiency in the patient. That therapeutic approach is akin to the use of L-dopa in Parkinson's disease and acetylcholine precursors in

Alzheimer's disease. Unfortunately, while the former has proved therapeutically successful in Parkinson's, precursor therapy failed in Alzheimer's. As I discussed in my first report, this failure furthered the prevailing skepticism of an approach, like cholinesterase inhibitors, that depended upon functioning presynaptic cholinergic neurons, and instead favored alternative approaches such as postsynaptic muscarinic receptor agonists or metabolic enhancers. In sum, I do not believe that Dr. Davis's analogy was improper, and I believe that Dr. Domino's suggested alternative is not correct.

Date: September 11, 2006

EXHIBIT A

Documents

1. United Kingdom Patent No. 942,200
2. United States Patent No. 4,663,318
3. Letter from Frantsits and Mucke to Bonnie Davis re: galanthamine patents [SYN RAZ 0000181]
4. Letter from Bonnie Davis to Alfred Gagne re: support for claim of galanthamine's superiority in treatment of Alzheimer's disease [SYN RAZ 0017587]
5. Letter from Bonnie Davis to Dr. William Cressman re: enclosed "new set of materials on the use of galanthamine for Alzheimer's disease" [SYN RAZ 0000761 -763]
6. Shire complaint filed in Vienna Commercial Court [SYN RAZ-0018366 - 18374]]
7. Amendment [of patent application] responsive to office action of April 10 [JAN RAZ-0000031-0000039]
8. Physician's Desk Reference (2006)
9. Deposition transcript of Dr. Bonnie Davis (February 8-9, 2006) and Exhibits

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EXHIBIT F

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

IN RE: '318 PATENT INFRINGEMENT LITIGATION	)	Civil Action No. 05-356-KAJ (Consolidated)

SECOND EXPERT REPORT OF DR. HOWARD M. FILLIT

I. INTRODUCTION

1. This report supplements my opening expert report of July 28, 2006. In this report, I was asked by Plaintiffs to review the opinions set forth in the reports by Drs. Edward Domino and Allan Levey in this case and to set forth my own opinions concerning the validity of U.S. Patent No. 4,663,318 ("the '318 patent") in view of the defendants' claims that the patent is invalid due to anticipation, obviousness, or lack of enablement.

2. In forming the opinions set forth in this report, I have relied upon my experience and knowledge of the relevant literature and state of the art and reviewed the Domino and Levey reports, the documents discussed in those reports, and the materials referenced in my opening report and in Exhibit A to this report.

II. LEGAL STANDARDS

3. In order to assist me in evaluating the defendants' experts' reports and in forming my own opinion concerning the validity of the patent, I have been informed of the legal standards governing anticipation, obviousness, and enablement.

A. Anticipation

4. I have been informed that the statutory requirement for anticipation of a patent claim is that the claimed invention must be shown to be "known or used by others in this

country, or patented or described in a printed publication in this or a foreign country, before the *invention thereof by the applicant for patent.*" 35 U.S.C. § 102(a). Defendants' experts have asserted that the '318 patent was anticipated by an article published before Dr. Davis applied for her patent – P.A. Bhasker, "Medical Management of Dementia," The Antiseptic, 71: 45-47 (1974) (the "Bhasker article"). In order for that article to anticipate claims 1 and 4 of the '318 patent, I understand that this article must describe the invention claimed in those patent claims. That is, the article must describe, to one of ordinary skill in the art, each and every element of those claims.

5. Moreover, in order for the article to qualify as a "printed publication," I understand that the Bhasker article must be "publicly accessible." That is, it must be accessible to persons skilled or interested in the art. I understand that indexing of the article is relevant to determining whether it was accessible to persons skilled or interested in the art.

B. Obviousness

6. I have been informed that the following factors are relevant in determining whether a patent is invalid for reasons of obviousness: (1) the scope and content of the prior art; (2) the differences between the patented invention and the prior art; (3) the level of ordinary skill in the art; and (4) objective considerations of non-obviousness. I note that objective considerations of non-obviousness were addressed in my opening report. In forming my opinion, I have also been asked to consider whether the prior art would have provided a person of ordinary skill a motivation to combine or modify the prior art references so as to arrive at the claimed invention and also whether it would have provided such a person with a reasonable expectation of success in doing so.

C. Enablement

7. I understand that to be valid, a patent must enable one skilled in the art to make and use the claimed invention. A patent is enabling even if some experimentation is required, as long as it is not unduly extensive.

III. LEVEL OF ORDINARY SKILL IN THE ART

8. In forming the opinions expressed in this report, I have used the level of skill proposed by Drs. Domino and Levey, namely, "an M.D. or Ph.D. interested in the field of Alzheimer's disease research … who, as a result of such training and/or interest, would have knowledge of the cholinergic hypothesis of Alzheimer's disease, the role of acetylcholine in memory, and pharmacological strategies and approaches for treating Alzheimer's disease and related dementias." (Domino ¶ 30; Levey ¶ 19). As a medical doctor actively engaged in Alzheimer's research in January 1986, I believe I would meet this definition, and I worked closely with others who would too. I believe I have a good understanding of the knowledge and thinking of such a person at that time.

9. I note, however, that in my opinion, the level of skill deemed "ordinary" by Drs. Levey and Domino is overstated. At the time, Alzheimer's research was a specialized field. The "ordinary" person interested in methods of treating Alzheimer's disease – who I assume would be the relevant readership for Dr. Bonnie Davis's patent on using galantamine to treat that disease – would have been a treating physician. In 1986, such a person would not likely have had experience with Alzheimer's research. However, for purposes of forming the opinions expressed in this report, I have used the level of skill set forth in the reports of Drs. Levey and Domino, because the difference does not alter my conclusions.

IV. ANTICIPATION

10. I disagree with the assertions contained in Drs. Levey's and Domino's reports that the Bhasker article anticipates the claims of the '318 patent. In my opinion, these assertions rely upon a wholly unreasonable reading of the Bhasker article, which in fact teaches that "progressive dementias" – a category that Drs. Levey and Domino treat as encompassing AD – are untreatable. Bhasker at p. 45 ("With regard to progressive dementia, there appears very little to offer. Only management and no treatment is possible.").

11. The Bhasker article's single reference to galantamine (along with neostigmine) appears in connection with treating "local brain damage like tumour, head injury, infarct, etc." (p. 46). AD is not a form of local brain damage like tumour, head injury, infarct, or the like. A clinician or Alzheimer's researcher would read Bhasker as suggesting galantamine for forms of local brain damage. He or she would not understand the article to be suggesting galantamine for AD.

12. This understanding of the Bhasker article would be reinforced by the article's reference to the work of Dr. Alexander Luria. Dr. Luria was a Soviet neurologist known for his work in treating neurological disorders associated with tumor or local brain injury (that is, traumatic encephalopathy). I am not aware that he ever studied Alzheimer's disease; an ordinary clinician or Alzheimer's researcher would certainly not have thought of him in connection with such work. Instead, Bhasker's reference to Luria would have underscored to the skilled reader that the article's reference to galantamine was made in connection with local brain damage.

13. This understanding of the Bhasker article would also be reinforced by the fact that the Bhasker article refers jointly to galantamine and neostigmine in discussing the "deinhibitory process" said to be useful in treating local brain damage. It is true that galantamine was known to have certain therapeutic uses in common with neostigmine, such as "an antagonist of non-

depolarizing muscle relaxants." M. Bretagne, et al., "Essais Cliniques en Anesthesiologie d'un Nouvel Anticholinesterasique la Galanthamine," Anesthesie Analgesie Reanimation, 1: 285-92 (1971) (Translation at JAN RAZ 134055). Thus, the Bretagne reference finds both galantamine and neostigmine useful in reversing the paralyzing effects of curare. However, as a quaternary ammonium derivative, neostigmine does not pass the blood-brain barrier, a limitation that one of ordinary skill would have recognized in 1986. For this reason, neostigmine would be recognized as useless for improving cholinergic activity within the brain: "Having a quaternary ammonium group, [neostigmine] cannot penetrate the blood-brain barrier and is therefore useless in combating the central effects of anticholinergic drugs." D.A. Cozanitis, "Galantamine Hydrobromide, A Longer Acting Anticholinesterase Drug, in the Treatment of the Central Effects of Scopolamine (Hyoscine)," Anesthetist, 26: 649-50 (1977), at p. 650. Hence, Bhasker's reference to using either neostigmine or galantamine for "deinhibition" could not reasonably have been read as referring to any central cholinergic effect, since neostigmine was known not to have any central effects. This would necessarily exclude treatment of conditions, such as AD, which are wholly central in nature.

14. In short, it is my opinion that no skilled reader of the Bhasker article would reasonably understand the article to suggest galantamine for AD.

15. In addition, I do not believe a reader of ordinary skill would have understood the Bhasker article to reference AD at all. The article divides dementia into two types – reversible and irreversible (or progressive). Needless to say, the former category does not include Alzheimer's disease: there is not a single case in the 100 years since the disease was first identified where Alzheimer's disease has been reversed – in fact, reversal of a patient's dementia

would disprove an initial diagnosis of AD. AD cannot fall within the category of "reversible" dementia.

16. As to the latter category of irreversible dementias, the Bhasker article states that "[t]he irreversible cases belong to the category of dementias where there is a progressive fall-out of neurons and the course of the illness is rapidly downhill." (p. 45). AD may progress steadily and relentlessly, but its course is not rapid. Quite the reverse, the disease often runs for more than a decade after first diagnosis before final demise. I do not believe any reasonable clinician or researcher in Alzheimer's disease would have described the course of AD in 1986 as "rapidly downhill" and similarly would not have understood Bhasker's reference to "irreversible" dementias with a rapid downhill course to encompass Alzheimer's disease. Instead, such a reader would have concluded that the Bhasker article simply does not address AD.

17. Dr. Levey suggests that any reference to irreversible dementias "necessarily includes the most prevalent of the irreversible dementias, Alzheimer's disease." (Levey ¶ 99). But that ignores both the time and place of the Bhasker article. While AD may now be recognized as the most prevalent form of dementia in the elderly, that recognition was only beginning to emerge in 1974, when the Bhasker article was published. It would have been entirely natural for an article published at that time to overlook AD. Indeed, I graduated from medical school in 1974, and as best I recall, I was not taught anything about the disease in school.

18. Moreover, recognition of Alzheimer's Disease was particularly slow to come in India, where the Bhasker article was written and published. At the time, and continuing to the present day, Alzheimer's disease is rarely diagnosed in India. As recently as the mid-1990s, I was asked to consult on an elderly patient, in India, who was suffering from mental confusion,

and I was flown to India for that purpose because of the lack of experience or expertise in India with diagnosis in senile dementia or Alzheimer's disease. A person of ordinary skill reading a 1974 article on dementia written and published in India would not be at all surprised that Alzheimer's disease was not addressed.

19. In this regard, it is worth noting that the Bhasker article is published in a journal entitled The Antiseptic. Authors typically select journals in which to publish on the basis of subject matter and readership. Alzheimer's disease has nothing to do with microbial infection; its treatment does not involve antiseptics or antimicrobials.

20. In addition, the Bhasker article was not accessible to persons of ordinary skill in the art in 1986. The journal in which it appeared, The Antiseptic, is not a reference that researchers in the Alzheimer's field (let alone treating physicians with an Alzheimer's patient) would have reviewed in the ordinary course.

21. Moreover, a researcher working in Alzheimer's drug development in 1986 would not have found the Bhasker article through the normal channels of scientific research. Such a researcher would have used a medical index and would have reviewed the relevant, standard scientific journals. These techniques would not have led a researcher in Alzheimer's disease, much less a clinician, to find the Bhasker article. In 1986, the standard index – the Index Medicus, a monthly guide to articles published in approximately 4,000 journals – did not include The Antiseptic. And as far as I am aware, the Bhasker article was not cited by any relevant scientific literature at the time.

22. Finally, the title of the journal would itself further discourage finding the article. A person of ordinary skill searching for articles concerning either galantamine or Alzheimer's disease would be highly unlikely to look in a journal entitled The Antiseptic. As noted,

Alzheimer's disease does not involve microbial infection. Galantamine is not an antiseptic or antimicrobial. Given the vast amount of literature published in journals potentially bearing on a pharmacologic investigation of Alzheimer's disease, I cannot imagine that a clinician or Alzheimer's researcher seeking a treatment of Alzheimer's disease would have had any occasion to review The Antiseptic. Despite working for 25 years in the Alzheimer's field, during which time I reviewed thousands of articles in hundreds of journals, I had never seen nor heard of The Antiseptic until this litigation.

V. NON-OBVIOUSNESS

A. Differences between the prior art and the patented invention

23. I understand that in reaching a conclusion about obviousness, the relevant inquiry is to compare the disclosures in the prior art, as they would be understood by one of ordinary skill in the art, to the claims of the patented invention. Those claims are described in my opening report. (See Fillit Report ¶¶ 19-23).

24. I believe that the invention claimed in the '318 patent differs from the prior art, as it would be understood by a person of ordinary skill, in at least two ways. First, the art as of January 1986 did not describe any drug as being a therapeutically effective method of treating Alzheimer's diease. Second, the art did not describe galantamine as a method for treating Alzheimer's disease.

25. I understand the reports of Drs. Domino and Levey to assert that physostigmine and tacrine had been shown by 1986 to be therapeutically effective treatments for Alzheimer's Disease. Dr. Levey goes so far as to assert that "[o]nce the physostigmine trials were known, it is not an exaggeration to say that it would have been obvious to anyone reading the literature that the ideal drug candidate for treating Alzheimer's disease would perform like physostigmine, but

without the drawbacks." (Levey ¶ 36). I find this an astonishing statement, one that is completely contradicted by the facts.

26. In the first place, I was just such a person who was following the physostigmine and other Alzheimer's disease literature in January 1986. Yet, not only was it not obvious to me that a drug like physostigmine would work, to the contrary I believed that the cholinesterase inhibitor approach was not working. In October 1985, I and several co-workers submitted a paper, published in 1986, in which we observed that acetylcholine precursor and cholinesterase inhibitor approaches to correcting the cholinergic deficit in AD had, for the most been "been unsuccessful or equivocal." H. Fillit, et al., "Observations in a Preliminary Open Trial of Estradiol Therapy for Senile Dementia-Alzheimer's Type," Psychoneuroendocrinology 11(3): 337-45 (1986), at p. 337. In addition, while we noted that "some benefit has been ascribed to cholinesterase inhibitors," those compounds "are limited by their low therapeutic ratio." (p. 337). Accordingly, we suggested estradiol as an alternative approach, which we believed looked promising in light of testing we had done on seven female patients with Alzheimer's Disease. Yet, even here, we warned not to draw any firm conclusions about efficacy, and we cautioned that "controlled clinical trials are needed to further define the potential therapeutic role for estradiol in postmenapausal women with SDAT." (p. 343).

27. The fact that we were proposing estradiol as "[a]n alternate approach to modifying this central cholinergic deficit" in AD, and actually testing it on Alzheimer's patients (p. 337), demonstrates that it was not obvious to us that a cholinesterase inhibitor approach was a therapeutically effective strategy for treating Alzheimer's Disease, let alone – as Dr. Levey would have it – that a cholinesterase inhibitor was "the ideal drug candidate for treating Alzheimer's disease." (Levey ¶ 36).

28. Nor was I alone in my skepticism of cholinesterase inhibitors. As I discussed in my opening report, there was considerable skepticism in the Alzheimer's field at the time of a cholinesterase inhibitor approach to treating the disease. Indeed, the many clinical trials conducted of other approaches, including muscarinic agonists and metabolic enhancers, demonstrates clearly that many in the field did not view cholinesterase inhibitors as the right aproach.

29. Even the articles Drs. Domino and Levey cite in support of their assertions do not describe cholinesterase inhibitors as therapeutically effective. For example, in R. Mohs, et al., "Studies of Cholinergic Drug Effects on Cognition in Normal Subjects and Patients with Alzheimer's Disease," Aging 17: 225-30 (1981), the authors conclude to the contrary that "[a]t present it is not clear whether studies of cholinergic drugs will lead to useful treatments for any of the debilitating dementias that afflict so many people." (p. 229). And in R.C. Mohs, et al., "Clinical Studies of the Cholinergic Deficit in Alzheimer's Disease," J. Amer. Geriatrics. Soc. 33(11): 749-57 (1985), the authors again express skepticism that a cholinergic approach such as a cholinesterase inhibitor would prove clinically beneficial:

> Combining careful biologic assessment and clinical diagnosis with attention to the unique pharmacologic properties of cholinergic drugs may ultimately identify a group of AD/SDAT patients who can derive meaningful clinical benefit from cholinesterase inhibitors or choliergic agonists. However, it must be recognized that even when these conditions are met, the use of such drugs could be severely limited. It has been pointed out, for example, that cholinergic cells have relatively few postsynaptic projections that are nonoverlapping, so that it is difficult for surviving cholinergic cells to compensate functionally for lost cells by increasing their firing rate. In addition, none of these drugs may be able to duplicate the phasic action of cholinergic cells in transmitting information. If such considerations prove to be true then any pharmacotherapy of AD/SDAT may have to depend on manipulation of transmitters and cotransmitters operating at sites postsynaptic to the dying neurons. (p. 756)

30. To similar effect is: B.S. Greenwald, et al., "Neurotransmitter Deficits in Alzheimer's Disease: Criteria for Significance," J. Amer. Geriatrics Soc., 31(5): 310-16 (1983):

"while it is generally agreed that L-dopa and other agonists can ameliorate symptoms in [Parkinson's Disease] patients, the effects of cholinergic-enhancing compounds in AD are much more limited. Encouragingly, positive effects of cholinomimetics have been reported; however, a level of clinical utility has not been achieved." (p. 313) And C. Johns, et al., "The Cholinergic Treatment Strategy in Aging and Senile Dementia," Psychopharmacology Bulletin, 19(2): 185-197 (1983): "The success of cholinomimetic treatment strategies thus far has been modest, and definitive treatment of SDAT awaits clarification of complex neurochemical variables, delineation of parameters that can predict response, and development of appropriate safe, long-acting pharmacologic agents." (p. 193).

31. In my opinion, a person of ordinary skill in the art would not understand the articles cited by Drs. Levey and Domino to be describing a cholinesterase inhibitor strategy generally or any particular cholinesterase inhibitor specifically as therapeutically effective for the treatment of Alzheimer's disease. This is confirmed, in my opinion, by the prevailing skepticism of cholinesterase inhibitors at the time and the preference for other approaches, as I reviewed in my opening report.

B. Motivation to Combine

32. In my opinion, the prior art also did not provide a person of ordinary skill in the art with the motivation to combine the references so as to conclude that galantamine could be a treatment for Alzheimer's disease. In addition to the limitations in the prior art concerning the cholinesterase inhibitors physostigmine and tacrine outlined above, the pharmacologic properties of galantamine known at the time would have made it appear unsuitable for use in treating Alzheimer's disease. Certainly, it would have appeared less suitable than physostigmine or tacrine, which were viewed as flawed, as Dr. Domino acknowledges. (E.g., Domino ¶ 43 ("it

was also recognized that physostigmine's and tacrine's usefulness as a long-term treatment for Alzheimer's disease was limited by its pharmacology")).

33. Galantamine is very different chemically from physostigmine and tacrine, with a different molecular structure. (See Domino ¶ 39). Such differences in the chemistry and molecular structure between drug substances can impact their pharmacologic properties, as a person of ordinary skill would recognize. In the case of galantamine and physostigmine, differences in their chemical structures would have cast much doubt on the simple substitution of one for the other.

34. In addition to these differences in chemistry, galantamine is a much weaker cholinesterase inhibitor than physostigmine, tacrine, or other cholinesterase inhibitors. Several researchers had made rough calculations of galantamine's relative potency by the time of the '318 patent application. In 1962, Boissier and Lesbros published an article in which they calculated that galantamine hydrobromide was 400-1000 times less active than neostigmine. J. Boissier and J. Lesbros, "La galantamine, puissant cholinergique naturel. II-Activite anticholinesterasique de galanthamine et de quelques derives," Ann. Pharm. Fr. 2: 150-55 (1962) (Translation at SYN RAZ 0022935). In 1965, Nesterenko measured the relative potencies of physostigmine and galantamine, and concluded that doses of galantamine needed to to 10-12 times higher than for physostigmine to achieve similar levels of cholinesterase inhibition. L.N. Nesterenko, "Effect of Galantamine on the the Acetylcholinesterase Activity of Various Regions of the Brain," Farmakol. I Toksikol. 28(4): 413-14 (1965) (Translation at SYN RAZ 0013374). And, finally, in 1976, Tonkopii et al. compared the action of galantamine and tacrine on acetylcholinesterase from human erythrocyte and from brain slices of various animals, and they concluded that galantamine was about 100 times weaker against acetylcholinesterase than

physostigmine. V. D. Tonkopii et al., "Interaction of Reversible Inhibitors with Catalytic Centers and Allosteric Sites of Cholinesterases." Bull. Exp. Biol. Med. 86: 400-01 (1976) (Translation at SYN RAZ 0013159).

35. Such calculations were not obscure: it was well-known in the scientific literature by 1986 that galantamine was a relatively weaker inhibitor of cholinesterase, as reflected by roughly contemporaneous publications: D.S. Paskov, "Galantamine," in D.A. Kharkevich (ed.) New Neuromuscular Blocking Agents, Vol. 79, Handbook of Experimental Pharmacology, pp. 653-72 (1986), at 654. ("The inhibitory effect of galanthamine on acetylcholinesterase . . . was found to be considerably lower than that of physostigmine and neostigmine."); D. Mihailova et al., "Modeling of Pharmacokinetic and Pharmacodynamic Behavior of Nivalin in Anaesthetized Cats," Methods Find. Exptl. Clin. Pharmacol. 11: 595-601 (1985) (noting the weakness of galantamine's anticholinesterase effect). Thus, it is my opinion that a person of ordinary skill in 1986 would have recognized galantamine's relatively weak potency.

36. This recognition of galantamine's weak potency would have discouraged drug developers from recognizing or developing it as a treatment for Alzheimer's disease. In fact, the literature expressed a concern that other cholinesterase inhibitors would not be effective because they were not potent enough – they did not achieve sufficient levels of cholinesterase inhibition. In 1985, Mohs et al., for example, expressed the view that high levels of cholinesterase inhibition correlated with beneficial results in the treatment of Alzheimer's disease. They wrote: "Improvement on memory tests while receiving physostigmine was highly correlated with the percent of inhibition in CSF: The patients who improved up to 40% on certain memory tests had a very high degree of cholinesterase inhibition, and patients with smaller improvements also had

a smaller percent of cholinesterase inhibition." R.C. Mohs et al., "Oral Physostigmine Treatment of Patients With Alzheimer's Disease," Am. J. Psychiat. 142: 28-33 (1985), at 32.

37. The weak potency of galantamine would have given rise to yet another concern discouraging its use for Alzheimer's disease: that any potentially therapeutic dose of galantamine would have serious safety and tolerability issues, because higher doses would need to be given in order to achieve efficacy. This concern would only have been increased by galantamine's established peripheral effects. The Pernov article cited by both Drs. Domino and Levey, K.G. Pernov, "Nivalin and its Curative Effect Upon Diseases of the Nervous System," Psychiatry, Neurology and Medical Psychology Bulletin on Research and Practice, 13(11)" 416-420 (1961) (cited at Domino ¶¶ 37, 87; Levey ¶¶ 81, 83, 103, 115-116), for example, describes galantamine as treatment for "**above all** diseases of the neuromuscular apparatus … and disease of the peripheral motoric neurons." (Mylan(GAL) 05984) (emphasis added). M. Bretagne, et al., "Essais Cliniques en Anesthesiologie d'un Nouvel Anticholinesterasique la Galanthamine," Anesthesie Analgesie Reanimation, 1: 285-92 (1971) (cited at Levey ¶ 83, translation at JAN RAZ 0134055-61) notes that, as a cholinesterase inhibitor, "the activity of Galanthamine is relatively weak compared with that of neostigmine and [physostigmine]" and the authors suggest that its quick action in reversing curare paralysis may be due to the fact that "Galanthamine directly excites smooth muscle and striated muscle." (JAN RAZ 0134058). While we now know that galantamine in fact has an allosteric modulatory effect on the nicotinic receptor, this was unknown at the time, and these statements would instead have suggested that galantamine's principal action was peripheral, a highly undesirable feature for treatment of AD.

38. Not only was galantamine recognized as being a weaker cholinesterase inhibitor, its duration of action would not have been viewed in 1986 as meaningfully longer than

physostigmine or tacrine for purposes of treating a steadily progressive dementia such as AD. The pharmacokinetics of galantamine, particularly orally administered galantamine, does not appear to have been systematically studied before January 1986. What was published does not suggest that galantamine's half-life was particularly long. Bretagne, et al. (1971) states that at equivalently effective doses, "[g]alanthamine is faster in onset and **more transient in duration than that of neostigmine**." Bretagne et al., "Essais Cliniques en Anesthesiologie D'un Nouvel Anticholinesterasique la Galanthamine," Anesthesie Analgesie Reanimation, 1: 285-92 (1971) (JAN RAZ 0134057 (emphasis added)). For duration, they report simply that "the action of this product [galantamine] persists for over two hours." (JAN RAZ 0134061).

39. Yet, with regard to physotigmine's duration of action, R.C. Mohs et al. (1985) had similarly reported that "studies of orally administered physostigmine in patients with ataxia suggest that steady-state levels can be achieved with dosing every 2 hours." R.C. Mohs et al., "Oral Physostigmine Treatment of Patients With Alzheimer's Disease," Am. J. Psychiat. 142: 28-33 (1985), at p. 28. Similarly, Thal et al. (1983), had observed that "the biologically effective half-life of orally administered physostigmine is undoubtedly much longer than previously suspected." L.J. Thal et al., "Oral Physostigmine and Lecithin Improve Memory in Alzheimer's Disease," Ann. Neurol. 13: 491-96 (1983), at p. 495.

40. The articles Drs. Domino and Levey cite for the proposition that galantamine was longer acting than physostigmine arise in the context of conditions, such as scopolamine-induced amnesia, which are temporary in nature and involve acute rather than chronic administration of therapy. The pharmacologic considerations for such treatments are very different than those for treatment of AD. Suggestions that galantamine is a longer-acting or appropriate substitute for physostigmine in the context of such temporary or acute conditions would not lead one of

ordinary skill to conclude the galantamine was also a sufficiently long acting or appropriate substitute for physostigmine in the very different context of Alzheimer's Disease.

41. I believe that a person of ordinary skill, reviewing the relevant literature available in 1986, would not have concluded that galantamine's duration of action was sufficiently long to overcome any perceived deficiencies in physostigmine's duration of action – especially when combined with galantamine's significant perceived disadvantage, its weaker cholinesterase inhibitory effect.

42. In fact, Dr. Domino himself reached this conclusion in an article that he published in 1988. E.F. Domino, "Galanthamine: Another Look at an Old Cholinesterase Inhibitor," in Giacobini, E., and Becker, R., eds., Current Research in Alzheimer Therapy, pp. 295-303 (1988). In this article, Dr. Domino reviewed the pharmacokinetics of galantamine for purposes of evaluating the drug's potential for use in treating AD and concluded that galantamine was "**not a very long acting compound**" and was "**only as long acting as physostigmine but much less potent**." (p. 301 (emphasis added)).

43. As a final note, none of the physostigmine or tacrine references cited by Dr. Levey or Dr. Domino actually suggest modifying the existing cholinesterase inhibitor approach by using galantamine. The references express the view that the efficacy of physostigmine and tacrine was limited, but did not propose that new cholinesterase inhibitors should be attempted. (The prevailing view was that if improvements were to be made, such improvements likely would come through efforts to develop entirely new cholinergic drugs.) For example, R. Mohs, et al. (1981) stated expressly that "no safe long-acting cholinesterase inhibitor is available at the present time." R. Mohs, et al., "Studies of Cholinergic Drug Effects on Cognition in Normal Subjects and Patients with Alzheimer's Disease," Aging 17: 225-30 (1981), at p. 226-227. And

B.S. Greenwald, et al. (1983) similarly warned that "currently available cholinergic agents are unable to substantially influence symptoms of AD." B.S. Greenwald, et al., "Neurotransmitter Deficits in Alzheimer's Disease: Criteria for Significance," J. Amer. Geriatrics Soc., 31(5): 310-16 (1983), at p. 313. These are articles from some of the leading figures in Alzheimer's research, and I do not believe that a person of "ordinary" skill would have ignored these express warnings in the very articles Drs. Domino and Levey cite on physostigmine in order to arrive at the conclusion that the old, weak cholinesterase inhibitor galantamine was a promising or even suitable substitute for physostigmine in treating AD. To the contrary, these statements would have instead further discouraged a person of ordinary skill from modifying those references to use galantamine in lieu of physostigmine or tacrine.

C. Reasonable Expectation of Success

44. The foregoing makes it clear to me that a person of ordinary skill in the art in January 1986 would have not had a reasonable expectation of success in using galantamine to treat Alzheimer's disease, even if such possible therapeutic use had occurred to him or her. The results of the studies on physostigmine did not establish proof of concept that cholinesterase inhibitors would work in treating Alzheimer's Disease; the outcomes of those trials were equivocal and inconsistent. If anything, the clinical trial results of physostigmine would have led a person of ordinary skill to conclude that galantamine would have an even lesser chance of success, because it is "only as long acting as physostigmine but much less potent." E.F. Domino, "Galanthamine: Another Look at an Old Cholinesterase Inhibitor," in Giacobini, E., and Becker, R., eds., Current Research in Alzheimer Therapy, pp. 295-303 (1988), at p. 301. And of course, physostigmine had not succeeded.

45. My opening report further supports the fact that a person of ordinary skill would not have had a reasonable expectation that galantamine would successfully treat Alzheimer's

disease. That researchers were skeptical of a cholinesterase inhibitor approach to the treatment of Alzheimer's disease cuts directly against a reasonable expectation of success for galantamine.

VI. ENABLEMENT

46. Dr. Levey's report also claims that the '318 patent does not "enable" the patented invention because the patent does not disclose sufficient information to show that galantamine would be a therapeutically effective treatment for Alzheimer's disease. (Levey ¶ 120). I disagree. Dr. Davis's patent discloses sufficient information such that a person of ordinary skill could make or use her invention.

47. In particular, the patent tells a researcher what steps that he or she should take in order to implement Dr. Davis's invention. The patent describes the animal testing needed to confirm the efficacy of galantamine in the treatment of Alzheimer's disease:

> The following test provides a good animal model for Alzheimer's disease in humans: A selective lesion is placed in a subcortical nucleus (nucleus basalis of Meynert) with a resultant cortical cholinergic dficiency, similar in magnitude to that seen in early to moderate stage Alzheimer's disease. . . . Drugs that can normalize these abnormalities would have a reasonable expectation of efficacy in Alzheimers' disease. ('318 patent, p. 2, column 2, ll. 45-54).

48. Based on my experience in drug development, I agree that these animal tests would be the logical next step, in 1986, to confirm the utility of galantamine to treat Alzheimer's disease. The patent thus describes for a person of ordinary skill how to best confirm – short of conduct human trials – the therapeutic activity of galantamine described in the patent.

49. Both Drs. Domino and Levey further assert that claim 4 of the patent is not enabled because there is "no support for any dosage of galantamine at the high end of her range." (Levey ¶ 121; see also Domino ¶ 97). But a person of ordinary skill reading the '318 patent would have been aware of how to arrive at the correct dosage of galantamine. That is, he or she would have titrated the dose – a standard clinical practice in which a patient is started

conservatively with a low dosage, which is then slowly increased to arrive at a therapeutically effective dosage range. The patent itself refers to this technique. (See '318 patent, col. 1, lns. 64-66) ("It may be necessary to begin at lower doses than are ultimately effective."). In my opinion, the patent provides sufficient information to enable a person of ordinary skill to determine an appropriate dose range for galantamine.

VII. MISCELLANEOUS

50. Finally, I note that both Dr. Levey and Dr. Domino criticize the way that the '318 patent was prosecuted in the Patent Office. I do not understand that the manner in which a patent is prosecuted to be relevant to the questions of anticipation, obviousness, and enablement that the defendants are raising in this case. I am also not an expert in patent prosecution. However, based on my review of the patent prosecution from the standpoint of an expert in drug discovery and development in the Alzheimer's field, I do not agree with Dr. Levey's or Dr. Domino's criticisms. In my opinion, the statements made to the Patent Office were scientifically fair and reasonable.

51. For example, both Dr. Levey and Dr. Domino criticize Dr. Bonnie Davis for failing to cite the Bhasker article to the Patent Office. (Levey ¶ 125; Domino ¶ 63). I find this criticism absurd. As I discussed above, a reasonable scientist would not have read the Bhasker article as having anything to do with Alzheimer's disease; it is Dr. Levey's and Dr. Domino's purported reading of the Bhasker article that is unreasonable.

52. In addition, I understand from Dr. Bonnie Davis's deposition that she was not even aware of the Bhasker article at the time she obtained the patent. I find this too entirely reasonable. Again, as discussed above, the Bhasker article had never been indexed or cited at the time the patent was prosecuted, and was published in an obscure journal, The Antiseptic, that no one researching Alzheimer's disease at the time would have thought to review in the course of

his or her research. I am not aware that either Dr. Levey or Dr. Domino ever cited the Bhasker article in any of their publications on Alzheimer's disease – why then would they expect Dr. Bonnie Davis to have done so?

53. Second, both Dr. Levey and Dr. Domino take Dr. Bonnie Davis to task for purportedly failing to inform the Patent Office of the cholinergic hypothesis of Alzheimer's Disease. Dr. Domino asserts, for example, that "she completely ignores the cholinergic hypothesis of Alzheimer's disease" and fails to discuss the physotigmine work conducted by Dr. Ken Davis and others. (Domino ¶ 59; see also Levey ¶ 126). But this assertion is plainly contradicted by the patent itself and by the document entitled "Amendment Responsive to Office Action of April 10, 1986," which I understand was submitted to the Patent Office in connection with prosecuting the '318 patent in September 1986.

54. First, in column 2 of her patent, Dr. Bonnie Davis expressly references the "central cholinergic deficiency" in mild to moderate Alzheimer's disease in proposing a "good animal model" for the disease. The patent states:

> The following test provides a good animal model for Alzheimer's disease in humans: A selective lesion is placed in a subcortical nucleus (nucleus basalis of Meynert) **with a resultant cortical cholinergic deficiency, similar in magnitude to that seen in early to moderate stage Alzheimer's disease**. ('318 patent, col. 2, lns. 45-50 (emphasis added))

The patent thus clearly mentions the cholinergic deficiency associated with Alzheimer's disease and does so in the context of proposing an animal model for evaluating pharmacologic treatments.

55. In addition, Dr. Bonnie Davis' September 1986 submission to the Patent Office provided further materials concerning the cholinergic hypothesis and its therapeutic implications. That document cites (on page 2) two review articles about Alzheimer's disease – one by

Hershenson & Moos and the other by Kendall – and I understand that copies of both those articles were submitted to the Patent Office with the document. Both those article discuss the cholinergic hypothesis, its potential utility in developing treatments for AD, and the work done on cholinesterase inhibitors (among other compounds) in connection with that hypothesis.

56. In addition, the same paragraph of Dr. Bonnie Davis' submission to the Patent Office also describes the physostigmine work, explaining that "although useful results have been reported in some cases by treatment with physostigmine, its poor therapeutic index is likely to preclude its widespread use and there is no generally effective treatment available." This description is entirely fair and, indeed, if anything more favorable than many of the judgments about physostigmine reviewed above. In fact, her judgment has been borne out by the passage of events, as physostigmine was never approved by FDA for treatment of AD (despite considerable effort by Forest Laboratories) and has never achieved widespread use for treatment of that disease.

57. Finally, Dr. Domino takes issue with Dr. Bonnie Davis' analogy to treatment of diabetes in her submission to the patent office, suggesting that the "proper analogy for galantamine … would have been for Dr. Davis to compare the effect of insulin in normal adults to the effect of insulin in diabetes." (Domino ¶ 58). But it is Dr. Domino's analogy which is incorrect. Diabetes is characterized by a degradation of the body's ability to produce insulin; treatment by insulin thus replaces the missing biological agent. The analogy to insulin in the AD context would be acetylcholine precursor therapy – also intended to replace the missing biologic agent (in AD, acetylcholine). Precursor therapy failed in the treatment of Alzheimer's disease, and this failure, as I explained in my opening report, only furthered the skepticism of a cholinergic approach to treatment of AD. I find nothing misleading about Dr. Bonnie Davis'

analogy, but it is certainly worth noting that even Dr. Domino's suggested alternative (that is, administration of the missing biologic agent) supports the validity of the '318 patent, since such administration (of acetylcholine precursors) did not work.

Date: September 11, 2006

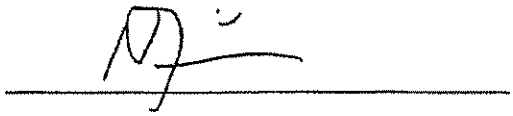

EXHIBIT A

Documents

1. United Kingdom Patent No. 942,200
2. United States Patent No. 4,663,318
3. Letter from Frantsits and Mucke to Bonnie Davis re: galanthamine patents [SYN RAZ 0000181]
4. Letter from Bonnie Davis to Alfred Gagne re: support for claim of galanthamine's superiority in treatment of Alzheimer's disease [SYN RAZ 0017587]
5. Letter from Bonnie Davis to Dr. William Cressman re: enclosed "new set of materials on the use of galanthamine for Alzheimer's disease" [SYN RAZ 0000761 -763]
6. Shire complaint filed in Vienna Commercial Court [SYN RAZ-0018366 - 18374]]
7. Amendment [of patent application] responsive to office action of April 10 [JAN RAZ-0000031-0000039]
8. Physician's Desk Reference (2006)
9. Deposition transcript of Dr. Bonnie Davis (February 8-9, 2006) and Exhibits

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EXHIBIT G

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EXHIBIT H

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